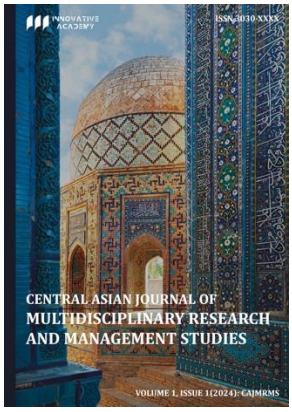

IMMUNOLOGICAL CHARACTERISTICS OF LATENT TUBERCULOSIS INFECTION

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ABSTRACT

Tuberculosis (TB) continues to be one of the top 10 causes of death worldwide, caused by Mycobacterium tuberculosis. According to WHO, in 2021, 1.4 million HIV-negative and 187,000 HIV-positive TB deaths were reported worldwide. Latent tuberculosis infection (LTBI) is an immune response against M. tuberculosis without clinical manifestations or radiological evidence of active TB. Current diagnostic methods are insufficient to differentiate between healthy and latently infected populations. Here, we used a machine learning approach to analyze publicly available proteomic data from saliva and serum in Ethiopia's healthy, latent TB (LTBI) and active TB (ATBI) people. Our analysis discovered a profile of six proteins, Mast Cell Expressed Membrane Protein-1, Hemopexin, Lamin A/C, Small Proline Rich Protein 2F, Immunoglobulin Kappa Variable 4-1, and Voltage Dependent Anion Channel 2 that can precisely differentiate between the healthy and latently infected populations. This data suggests that a combination of six host proteins can serve as accurate biomarkers to diagnose latent infection. This is important for populations living in high-risk areas as it may help in the surveillance and prevention of severe disease.

Mycobacterium tuberculosis (Mtb) is a major human pathogen that has resulted in one of the world's most serious public health problems. According to WHO, in 2021, 1.4 million HIV-negative and 187,000 HIV-positive TB deaths were reported worldwide. Globally, 10 million people develop tuberculosis (TB), and 1.6 million people die from the disease every year. Infections can be categorized as active TB (ATBI) or latent TB (LTBI). One-fourth of the world's population is latently infected with Mtb [1], and during their lifetime, approximately 5–15% of the LTBI-infected individuals (e.g., >70 million people) will develop ATBI disease when their immunity is compromised or suppressed (for instance, in the case of diabetes, HIV coinfection,

organ transplantation, and aging) [[1], [2], [3]]. Thus, the dynamic balance between the host immune system and bacterial pathogenicity determines the onset of 'reactivation' and clinical presentation of TB disease. Currently, in the absence of reliable control measures for TB, eradicating LTBI is a cornerstone of global TB control [4]. Achieving a better understanding of LTBI and subsequent reactivation is a research priority [5].

Although the incidence of active TB has declined recently in most high-income countries, the prevalence of LTBI has remained stable. Despite the historic decline, the incidence of active TB has reversed in the UK in the last 30 years and has become an area of concern for public health with the increase predominantly among the foreign born people in the UK. Appropriate screening therefore remains important because of the rising number of people travelling from high endemic areas and also because of the increasing use of immunosuppressive therapies. The magnitude of the reactivation of TB risk varies among high-risk categories; however, early diagnosis of LTBI may prevent the development of active TB. A systematic approach to managing LTBI in cohorts at high-risk reactivation is a critical component of the World Health Organization (WHO) End TB Strategy. Consequently, many countries have introduced LTBI control programmes targeting high-risk groups and screening to identify those with LTBI as well as TB.

Mtb infection depends on its initial encounters with host innate immune cells such as macrophages, neutrophils, dendritic cells, and natural killer (NK) cells. Following the Mtb infection, the host orchestrates a cascade of innate immunity defence functions via various pattern recognition receptors (PRRs) that activate phagocytosis, autophagy, apoptosis, and inflammation (Kleinnijenhuis et al., 2011). Depending on the cell type, the host targets different receptors or their combinations to detect and phagocytose Mtb. Apoptosis and autophagy are natural defence processes in macrophages that function to eradicate microbial infection and invasion. Mtb prevents these two processes to survive and remain dormant.

Mtb is also capable of regulating phagosomal development, preventing it from fusing with the lysosome, and decreasing the maximum acidity of phagosomal contents. Multiple genes work independently or in coordination to perform these functions. For instance, isocitrate lyase, the major enzyme in the glyoxylate (GLX) cycle, is encoded by the icl gene in Mtb. Isocitrate lyase is essential for Mtb latency and fatty acid utilization by bacteria and has been proposed as a potential therapeutic target for developing anti-TB drugs (Bhusal et al., 2017). When the carbon source that permits the Mtb growth reduces, icl enables the bacteria to use fatty acid as a carbon source and energy by using GLX. Further, it has been reported that the deletion of both icl1 and icl2 completely impaired intracellular replication of Mtb and caused its fast clearance from mice lungs. One of the characteristics of Mtb is its thick waxy coat-the unique cellular wall. The effectiveness of Mtb as a pathogen and its inherent resistance to numerous antimicrobial agents can be ascribed, in part, to its cell wall structure that possesses many efflux pumps and has limited permeability for numerous drugs (Jarlier and Nikaido, 1994). The treS gene in Mtb encodes the trehalose synthase (TreS) enzyme, which is an essential metabolite and serves critical functions in cell wall synthesis, glycolipid transport, and energy storage. However, a detailed review of all the crucial genes is beyond the scope of the review. The diverse functions of the genes involved in the latent stage of Mtb are shown in Table 1. Unequivocally, Mtb's metabolic capability and adaptability have contributed to its success as a pathogen during the inception of infection development and its persistence.

Conventionally, LTBI is identified by a host response to Mtb antigens using tuberculin skin testing (TST) or IFN-γ release assays (IGRA) [1]. However, neither test can accurately differentiate between LTBI and active TB nor resolve the various stages within the spectrum of Mtb infection [6,7]. It has recently become clear that LTBI is not a single entity but rather a broad spectrum of asymptomatic TB infection states that can be distinguished by different degrees of inflammation, bacterial replication, and host immunity [1]. These different states carry significantly different risks in reactivating TB. Thus, identifying individuals who have LTBI with economical, sensitive point-of-care (POC) diagnostics will enable medical staff to monitor these individuals to prevent disease progression, especially in developing countries. However, biomarkers that precisely differentiate healthy people from LTBI and/or ATBI are still lacking.

Biomarkers are of great importance in many fields, as they provide targets for the prevention, diagnosis, and treatment of multiple types of disease [8]. In recent years, machine learning has been used to analyze large datasets, such as DNA microarrays, RNA sequencing, proteomics, or metabolomics, to enable biomarker discovery in a data-driven manner [9]. While most studies rely on differential expression analysis to define fold and variant changes in large datasets, machine learning applies mathematical approaches to train a model to learn from the data and find biomarkers via classification and feature selection [10]. Herein, we used a machine learning approach to analyze previously published proteomic data from saliva and serum in Ethiopia's healthy, LTBI and ATBI people [11,12] and identified several proteins that can precisely differentiate between the healthy population and latently infected people.

Dataset, Input Features, and Classifiers. We have obtained sputum data from a previous study where we collected 25 LTBI, 19 control, and 31 Pulmonary Tuberculosis (PTB) samples [11]. Shotgun proteomics was used to identify 432 proteins in the 75 samples using the Proteome Discoverer platform (version 1.4, Thermo Scientific) and the Sequest HT algorithm [11]. Label-free quantification (LFQ) generates relative protein abundance data, which is further transformed into log (base 2) values. Two classifications between PTB, LTBI, and control cohort.

Four hundred thirty-two proteins were identified from the 75-person cohort, which consisted of PTB, LTBI, and control. We developed Random Forest prediction models for individual proteins and sorted the prediction scores for proteins using the Weighted Average MCC score; a higher MCC value signifies a more accurate model. Only Orosomucoid 1 (ORM1) has an MCC score (0.422) greater than 0.4, three proteins above 0.3, and 34 proteins above 0.2 MCC (Table S1). Next, we obtained a 2-protein.

The molecular identification of the stages of Tuberculosis disease is still a significant health problem. In our previous report, we observed that host proteins could be used to distinguish active pulmonary tuberculosis from latent and healthy individuals [11]. However, the distinction between a latently infected individual and their healthy counterparts is still difficult with current diagnostics. In this study, the first machine learning model we developed is to differentiate between PTB

References:

1. Shavkatovich, S. H. (2024). AN ORGAN-PRESERVING SURGICAL OPERATION FOR GENITAL PROLAPSE. *Journal of Advanced Scientific Research (ISSN: 0976-9595)*, *5*(1).

2. Shavkatovich, S. H. (2024). COMPLICATIONS DURING EMERGENCY CESAREAN SECTION OPERATION IN OBSTETRICS. *JOURNAL OF HEALTHCARE AND LIFE-SCIENCE RESEARCH*, *3*(2), 30-33. Shavkatovich, S. H. (2024). COMPLICATIONS DURING EMERGENCY CESAREAN SECTION OPERATION IN OBSTETRICS. *JOURNAL OF HEALTHCARE AND LIFE-SCIENCE RESEARCH*, *3*(2), 30-33.

3. Shavkatovich, S. H., & Negmadjanov, B. B. (2020). Optimization Of Pelvic Prolaps Surgical Correction Using Its Own Tissues. *The American Journal of Medical Sciences and Pharmaceutical Research*, *2*(12), 15-19.

4. Ташпулатова, Ф. К., & Абдусаломова, М. И. (2020). Частота и характер побочных реакций от противотуберкулезных лекарственных средств у больных детей туберкулезом. *Новый день в медицине*, (2), 544-547.

5. Ташпулатова, Ф. К., & Абдусаломова, М. И. (2020). Частота и характер побочных реакций от противотуберкулезных лекарственных средств у больных детей туберкулезом. *Новый день в медицине*, (2), 544-547.

6. Khomova, N., Tashpulatova, F., & Sultanov, S. (2017). Compliance-is patient adherence to treatment, as well as partnerships between doctor and patient.

7. Ташпулатова, Ф. К., Жалолов, А. Ж., Медведева, Н. В., & Долгушева, Ю. В. (2016). Уровень комплаенса у больных с лекарственно устойчивым туберкулезом. In *Медицина: вызовы сегодняшнего дня* (pp. 46-50).

8. Ubaĭdullaev, A. M., RSh, K., Stoianovskiĭ, E. A., & Ataullaeva, D. E. (2000). Tuberculosis epidemiology and disease control in Uzbekistan. *Problemy Tuberkuleza*, (3), 7-9.

9. Вахабов, А. А., & Ташпулатова, Ф. К. (2018). Поражение печени у больных туберкулезом легких при побочных реакциях от противотуберкулезных препаратов. *Молодой ученый*, (3), 91-93.

10. Хомова, Н. А., & Ташпулатова, Ф. К. (2018). Сравнительный анализ применения шкалы Мориски-Грин и опросника" Уровень комплаентности" в исследовании приверженности к лечению у больных туберкулёзом лёгких. *Вестник Авиценны*, *20*(2-3), 299-304.

11. Ташпулатова, Ф. К., & Дадаходжаева, Л. С. (2013). Применение фитоадаптогеннов в комплексной терапии у больных деструктивным туберкулезом легких. *Клиническая медицина Казахстана*, (2 (28)), 66-67.

12. Yusupbekov, A., Kanda, M., Usmanov, B., Tuychiev, O., Baymakov, S., Sakamoto, J., & Yusupbekov, A. (2020). Surveillance of Esophageal Cancer in the Republic of Uzbekistan from 2000 to 2018. *Asian Pacific Journal of Cancer Prevention: APJCP*, *21*(8), 2281.

13. Baymatovich, U. B., Axmedjanovich, Y. A., Vakhidovich, K. R., & Abdullaevna, I. U. (2016). Analysis of the surgical treatment of the pulmonary metastatic lesions. *European science review*, (3-4), 197-199.

14. Gayratovich, U. F., Dehkonovich, D. M., & Ahmedjanovich, Y. A. (2016). The modern principles of surgical treatment in non-organ retroperitoneal tumors. *European science review*, (3-4), 195-197.

15. Yusupbekov, A., Shinozuka, T., Juraev, E., Usmanov, B., Kanda, M., Sakamoto, J., & Tuychiev, O. (2024). Exacerbated prognostic impact of multiple intramural metastasis

versus single intramural metastasis of thoracic esophageal squamous cell carcinoma: evidence from an Uzbekistan cohort. *Surgery Today*, 1-8.

16. Еникеева, З. М., Агзамова, Н. А., Абдирова, А. Ч., Ибрагимов, А. А., Салихов, Ф. С., Ярашева, Н. И., ... & Тилляшайхов, М. Н. (2020). Республиканский специализированный научно-практический медицинский центр онкологии и радиологии, Ташкент, Узбекистан. *НАЦИОНАЛЬНЫЕ РЕДАКЦИОННЫЕ КОЛЛЕГИИ*, *8*(3).

17. Usmanov, B. B. (2015). Current strategies for diagnostics and treatment of lung and pleura metastasis. *Russian Journal of Oncology*, *20*(6), 46-50.

18. Baymatovich, U. B., Axmedjanovich, Y. A., Vakhidovich, K. R., & Abdullaevna, I. U. (2016). Analysis of the surgical treatment of the pulmonary metastatic lesions. *European science review*, (3-4), 197-199.

19. Khairuddinov, R., Usmanov, B. B., Rustamov, S. H., Madiarov, B. T., Juraev, E. E., Rasulov, A. E., & Djumanazarov, T. M. (2014). 414. Development and improvement of diagnosis and treatment of invasive esophageal cancer. *European Journal of Surgical Oncology*, *40*(11), S159.

20. Axmedjanovich, Y. A., Baymatovich, U. B., Vakhidovich, K. R., & Dilshodovich, T. O. (2019). Modern views in diagnostics and treatment of esophageal cancer (literature review). *European science review*, (3-4), 57-62.

21. Ibragimov, A. A., Enikeeva, Z. M., Agzamova, N. A., Madyarov, B. T., Usmanov, B. B., Amonov, A. I., & Pulatov, C. C. MECHANISM OF ANTINEOPLASTIC AND RADIOSENSITY ACTION OF THE PREPARATION K-26. In *XIII International Symposium on the Chemistry of Natural Compounds (ISCNC 2019)* (p. 102).

22. Yusupbekov, A. A., Usmanov, B. B., & Khakimov, Y. S. (2019). THE ROLE OF PARENTERAL CORRECTION OF HOMEOSTASIS IN SURGERY FOR CANCER OF THE ESOPHAGUS AND CARDIOESOPHAGEAL ZONE. *Toshkent tibbiyot akademiyasi axborotnomasi*, (4), 145-147.

23. Ismailov, S. I., Negmatov, J. B., Rashitov, M. M., Atadjanova, M. M., Allayarova, G. I., Muratova, S. T., ... & Elov, A. A. (2016). Universal salt iodization program in Uzbekistan: A cost-benefit analysis. *Europaische Fachhochschule*, (2), 21-24.

24. Ismailov, S., Yuldasheva, F., & Muratova, S. (2013, August). Level of iodine supply among the population of Tashkent region in the Republik of Uzbekistan. In *The 27th congress of the International Pediatric Association. Melbourne, Australia, 24* (p. 812).

25. Muratova, S. T. (2021). Диагностированные нарушения минеральной плотности костной ткани и уровней кальциотропных гормонов у детей с ювенильным гипертиреозом. *Modern Pediatrics. Ukraine*, (3 (115)), 23-30.

26. Muratova, S., & Alimov, A. (2020, August). Mineral density of bone tissue, parathyroid hormone and vitamin D in children and adolescents with thyrotoxicosis. In *Endocrine Abstracts* (Vol. 70). Bioscientifica.

27. Муратова, Ш. Т. (2017). Психоэндокринные нарушенияу подростков с болезнью Грейвса. *Международный эндокринологический журнал*, *13*(4), 271-275.

28. Muratova, S. (2023, May). A case of follicular thyroid cancer in a girl with Graves. In *Endocrine Abstracts* (Vol. 90). Bioscientifica.

29. Muratova, S., Alimov, A., & Azimova, S. (2022, May). Influence of the mother. In *Endocrine Abstracts* (Vol. 81). Bioscientifica.

30. Kholbaevich, K. G., Tursunkulovich, E. K., Khamrokulovna, E. Y., & Kayumkhodjaevich, A. A. (2020). Phenological phases and thermal mode of the winter wheat in the irrigated areas in the Fergana region. *International Journal of Psychosocial Rehabilitation*, *24*(5), 3833-3838.

31. Abdullaev, A. Q., Kholbaev, G. X., & Safarov, E. Y. (2009). Guidelines for the use of mathematical statistics, the use of computers and geographic information systems in finding related equations in agrometeorology. *T. GMITI*.

32. Kholbaev, G. K., & Abdullaev, A. K. (2020). Change of meteorological values in the autumn of Republic of Karakalpakstan and Khorezm region. *Change*, *7*(3).

33. Абдуллаев, А. К., Холбаев, Г. Х., Пулатов, У. Ш., Кутлимуратов, Х. Р., Абдумажитов, Д. И., & Султашева, О. Г. (2007). Многолетние значения метеорологических элементов по странам мира.

34. Kholbaevich, K. G., Kayumkhodjaevich, A. A. L., & Khamrokul, E. (2020). The vegetation period of winter wheat in southern areas of the Republic of Uzbekistan. *Journal of Critical reviews*, *7*(9), 122-125.

35. Абдуллаев, А. К., & Холбаев, Г. Х. (2005). Рис, пшеница и хлопковое волокно по странам мира. *Т.:. НИГМИ*.