MedCrave
Step into the World of Research
Journal of Microbiology & Experimentation

Mini Review
Open Access
CrossMark

Under diagnosis of tuberculosis in times of pandemic and the use of microRNAs as biomarkers of infection

Abstract

Objective: To analyze the evidence on the underdiagnosis of tuberculosis in the SARS-CoV-2 pandemic, the risk of COVID-19 morbidity and mortality in coinfection with Mycobacterium tuberculosis, and the use of microRNAs as diagnostic tools.

Material and methods: We used an adaptation of the Cochrane rapid review methodology. The search was performed in PubMed and was limited to August 3. Titles and abstracts were reviewed, and the full texts of the final selection were analyzed.

Results: The evidence found reports that in pandemic years there has been a decrease in the diagnosis of tuberculosis worldwide. In addition, the emergence of the TB-COVID-19 syndemic and its serious implications indicate that TB diagnosis should be prioritized.

Conclusion: As a result of the pandemic, there were serious disruptions in TB care and services, leading to underdiagnosis of TB cases. To know the implications of the TB-COVID-19 syndemic, more studies are needed in countries with a high burden of TB. On the other hand, several efforts are being made worldwide to find miRNAs as specific biomarkers that can be used for the molecular diagnosis of TB.

Keywords: diagnostics, *Mycobacterium tuberculosis*, SARS-CoV-2, microRNAs

Volume 10 Issue 5 - 2022

Elizabeth Castillo-Villanueva, Antonia Isabel Castillo Rodal
Department of Microbiology and Parasitology, School of Medicine, National Autonomous University of Mexico, Mexico

Correspondence: Antonia Isabel Castillo Rodal, Department of Microbiology and Parasitology, School of Medicine, National Autonomous University of Mexico, Avenida Universidad No. 3000. C.P.04510, Ciudad de México,
Email castillorodal@unam.mx

Received: October 01, 2022 | **Published:** October 12, 2022

Abbreviations: TB, tuberculosis; MTB, Mycobacterium tuberculosis; PNT, national tuberculosis program; LTBI, latent tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB), which mainly affects the lungs, although; it can also affect other organs of the human body.[1,2] The current pandemic caused by the SARS-CoV-2 coronavirus, first reported in Wuhan City, China, in December 2019,[3-6] has dominated our attention for the past two years, because it has brought serious consequences to human life and the global economy.[7] On the other hand, tuberculosis remains a dominant infectious disease worldwide that disproportionately affects the poor and has been, for many years, the leading cause of death in people with HIV.[8] There are several points in common between COVID-19 and TB, both mainly affecting the respiratory tract and transmitted through respiratory secretions or respiratory droplets.[9] The fight against both diseases has been based on early diagnosis, contact tracing and vaccination.[2] However, in the past two years the world has focused on the fight against the COVID-19 pandemic. The World Health Organization has reported that globally there has been a worrying decline in the number of diagnosed TB cases and patient care worldwide in 2020, especially in high TB burden countries, a 28% reduction was reported compared to 2019, which, consequently, may increase the number of TB deaths by more than half a million additional deaths.[7-10] Early diagnosis is critical in order to control the spread of the bacteria. An important reason for refocusing on TB diagnosis during the pandemic is because of the emergence of the TB-COVID-19 syndemic.[11] It is unclear what the implications of this syndemia are; however, one possibility is that TB-COVID-19 coinfection will lead to a worsening of the existing active TB condition or an existing MTB infection may increase the risk of severity in SARS-CoV-2.[11,12] Another concerning aspect of this syndemic, is the reported cases of reactivation of latent TB in post-COVID-19 patients,[13] as one-quarter of the world's population is estimated to be affected by latent TB.[14] For these reasons, simultaneous diagnostic testing for TB and COVID-19 is essential to ensure effective treatment for patients. In this review we have analyzed the consequences of underdiagnosis of tuberculosis in the SARS-CoV-2 pandemic, the risk of morbidity and mortality from COVID-19 in coinfection with Mycobacterium tuberculosis, and the use of microRNAs as potential diagnostic tools.

Current overview of tuberculosis

Human TB is the most lethal infectious disease in the world.[15] The latest estimates indicate that approximately 10 million people have been infected with M. tuberculosis, of which 90% of those affected are adults. TB causes 1.4 million deaths annually, including about 300 000 HIV-positive people. No country is exempt from the disease, and it is endemic in most of the world's poor countries. It is estimated that about one-third of the world's current population is infected with M. tuberculosis;[16] and 5-10% of these individuals will develop clinical symptoms of the disease in their lifetime.[2] In 2018, in the Region of the Americas, 22 900 deaths from TB were estimated, of which 26% (5900) corresponded to persons with TB and HIV coinfection; the countries with the highest number of reported cases being Brazil, Mexico, and Peru. In Mexico, the estimated case fatality rate for TB in 2018 was 8.6%,[17] this rate, is an indicator of access to timely diagnosis and adequate treatment of TB. In 2018, the estimated case fatality rate for the Region was 7.9%, which, compared to previous years, showed a downward trend. However, the COVID-19 pandemic has reversed years of progress in providing TB services and reducing the burden of disease. The number of newly diagnosed TB persons notified decreased 18% from 2019 to 2020, returning to the 2012 level. Globally, in 2020, an estimated 9.9 million people became ill with TB, returning to the 2017 level.[2] The pandemic, also impacted

negatively on case notification, where there was a 17% deficit on average and in the specific case of Mexico, it presented a 26% case notification deficit by 2020. [2,17,18] Within the Region of the Americas, Mexico is one of the countries with a high incidence of TB, with an estimated 31,000 cases in 2020.[2,18]

Tuberculosis has been the most contagious and deadly bacterial disease in the world, and to date, it continues to be a public health emergency. With the aim of ending the global TB epidemic, in 2014 the End TB Strategy was established by WHO; and in 2018, global commitments were signed as a result of the political declaration of the high-level meeting of the United Nations General Assembly on tuberculosis, which aims to eliminate TB as a public health problem. The goal is to have a 90% reduction in tuberculosis mortality; an 80% reduction in tuberculosis incidence, with a regional target of 5.6 new cases per 100,000 inhabitants. In this sense, the COVID-19 pandemic has had unprecedented negative effects on global health and economy, attracting the attention and resources of many other public health services, such as TB.[9] Areas of particular concern during this global emergency include de novo TB case detection and the continuity of treatment of TB patients.[19] The latest global TB report issued by WHO presents a bleak picture of the trajectory of the global TB epidemic, describing an annual decline in TB incidence, marked by a decrease in both diagnosis and case notifications, resulting in an increase in the number of deaths from TB infection.[20] In Mexico, between 23,000 and 37,000 new TB cases were reported for 2019 according to WHO figures.[2,17] The Ministry of Health, through the National Tuberculosis Program (PNT) in 2019, recorded 22 285 new cases, with a rate of 23 cases per 100 000 population.[21] Mexico is part of the WHO End TB Strategy, which aims to decrease the incidence rate of TB. However, not only was it not reduced in the country, but in 2019, before the COVID-19 pandemic, it increased 4.1% with respect to 2015. This increase in TB incidence is mainly due to the implementation of molecular and rapid diagnostic methods, such as XpertMTB/RIF tests [22,23] and/or increased transmission due to the persistent deterioration of socioeconomic systems and fragmentation of health systems, late diagnosis, and increased comorbidities and coinfections.[17,18,21] Regarding TB diagnosis, the National Tuberculosis Program (NTP) estimated that in 2019, 75.5% of the TB cases expected for this year were detected; however, for 2020, as of October there was a lack of TB case detection of 30%. This resulted in a reduction in reported cases in the country of 60.53% of the expected cases.[18,24] These statistics show that there was a decrease in the number of cases diagnosed in the country during the beginning of the pandemic.

The COVID-19 pandemic has surpassed all other health problems worldwide. There are numerous ways in which this will affect existing public health problems. If TB diagnostic programs are not reactivated, there may be serious consequences for undiagnosed TB patients worldwide, particularly in low- and middle-income countries where TB is endemic and health services do not have the resources or infrastructure to cope now with the TB-COVID-19 syndemic, which will be discussed later. The economic impact of the pandemic is expected to exacerbate at least two of the main determinants of TB incidence: poverty and malnutrition. Models suggest that there could be a spike of more than 1 million additional cases per year in the period between 2020 and 2025.[25] Another concern is that TB patients often have underlying comorbidities and lung damage that may make them prone to more severe COVID-19. The response to the COVID-19 pandemic has left us with several lessons, including that public health programs can be implemented quickly and relatively well coordinated, demonstrating that current programs can be improved to address TB.[26]

Morbidity and mortality risk due to TB-COVID-19 co-infection

It is estimated that about 25% of the world's population is infected with MTB. An untreated TB-infected person can infect 10 to 15 people per year. This happens through aerosols containing the bacillus, which are expelled from the host by coughing, sneezing, talking, singing and spitting. Of the infected cases, although a large proportion will not develop the active phase of the disease (resulting in latent TB, LTBI), the impact of active TB cases in terms of disability, care costs and deaths, among other aspects, is more than significant. However, despite its contagiousness and severity, TB is curable if diagnosed and treated in a timely and appropriate manner. Among the risk factors for a person to progress from LTBI to active TB are: being infected with HIV-AIDS (with greater risk if not receiving HIV treatment), having received a transplant (due to the immunotherapy received), silicosis, chronic kidney disease, diabetes mellitus, smoking and SARS-CoV-2 infection.[13,15] Currently, the two leading causes of death among infectious diseases are TB and COVID-19, there are a growing number of studies attempting to elucidate the interactions between MTB and SARS-CoV-2. Early reports point to worsening respiratory symptoms in TB-COVID-19 coinfected individuals.[1,10,27,28] Disorders induced by each pathogen tend to induce an unbalanced inflammatory response, which may promote progression and worsening of both diseases.[12] Prior to COVID-19, TB-HIV syndemia was evident and reported worldwide, occurring in both adults and children, and has been one of the major obstacles to eliminating TB worldwide.[29,30] Overall, TB-COVID-19 syndemia has several possible implications including reactivation of TBL after SARS-CoV-2 infection, TB-COVID-19 co-infection which consequently may lead to aggravation of an existing active TB condition, may increase the risk of severity of SARS-CoV-2 infection.[11,12] Understanding the nature of the interactions between MTB and SARS-CoV-2 pathogens will be crucial for the development of therapeutic strategies against coinfection.

Traditional tuberculosis diagnosis and microRNAs as new tools

Currently, more than two billion people worldwide are living with latent Mycobacterium tuberculosis infection. Early diagnosis is critical in order to control the spread of the bacteria. Most people with TB disease have one or more of the following symptoms: weight loss, lack of appetite, night sweats, fever and fatigue. When the disease affects the lungs, symptoms of cough lasting more than 3 weeks, hemoptysis, and chest pain may be included.[2] All persons with these symptoms should be evaluated for TB disease. Traditional diagnostic tests for TB include the Mantoux tuberculin skin test and blood test by performing the interferon gamma release assay or IGRA, smear microscopy evaluation of the patient's specimen, accompanied by a physical examination and a chest radiograph. Currently, molecular tests of nucleic acid amplification and GeneXpert are also used; these tests have a high degree of sensitivity and confidence.[22,23,31]

Since 2010, the WHO has recommended the use of Xpert MTB/RIF for the diagnosis of pulmonary TB and in selected samples for the diagnosis of extrapulmonary TB.[32] The diagnosis of latent TB infection is made in persons without TB disease.[33] The diagnosis of latent TB infection is made by tuberculin skin test or IGRA assay, however, neither of these two assays is useful in being able to discriminate between latent or active TB, nor in being able to predict whether the patient who has latent TB will develop the active form of the disease.[34] In this context, it is imperative to apply versatile solutions and affordable tools to make a differential diagnosis between tuberculosis

Citation: Castillo-Villanueva E, Rodal AIC. Under diagnosis of tuberculosis in times of pandemic and the use of microRNAs as biomarkers of infection. *J Microbiol Exp*. 2022;10(5):156–160. DOI: 10.15406/jmen.2022.10.00368

and different respiratory pathogens, such as SARS-CoV-2 virus, and to discern between the different stages of tuberculosis disease. One of the most promising tools for the diagnosis and therapeutic follow-up of patients is the use of microRNAs as biomarkers of infectious diseases in blood.[35,36] miRNAs are small, non-coding RNAs, typically 18-24 nucleotides in size, that have an important role in regulating gene expression at the post-transcriptional level and are involved in shaping immunity by regulating gene expression in immune cells. To carry out their regulatory activities, miRNAs bind to their complementary sequence at the 3'untranslated end of the messenger RNA, targeting it for degradation or inhibiting its translation.[37,38]

Recent studies have established that the innate immune response against TB is significantly regulated by miRNAs.[39] In this sense, the analysis of the differential expression of miRNAs in samples from TB patients is an approach that is being studied to obtain biomarkers that allow us to discern between a healthy person and a person infected with latent or active TB, see Table 1.[2,35,39] For example, some of the miRNAs suggested to be used as biomarkers in TB infection and that have been characterized from patient blood samples are: miR-199b-3p, miR-199a-3p, miR-6886-3p, miR-486, miR-29, miR-21, miR-30 and miR-20 for active TB[35,36] and miR-6856-3p for latent TB infection,[36] to mention just a few. In another study, where they used microarrays and validated the results by qRT-PCR, they found five miRNAs (miR-424-5p, miR-365a-3p, miR-144-3p, miR-223-3p, and miR-451a-5p) with high expression in active TB vs. latent TB.[40] MicroRNAs have several attributes to be considered as potential biomarker molecules, the first being that the microRNA profile changes in response to treatment or stimuli.[36] Also, they are very stable molecules in blood, or in extracellular fluids,[16,41,42] for example, tumors send a considerable amount of microRNAs to the blood.[43] Several research groups have tried to identify well-defined microRNA signatures to be used as potential noninvasive biomarkers that could be analyzed in easily accessible specimens, with special attention to microRNAs circulating in blood, plasma, or in extracellular vesicles called exosomes.[16,44]

Table 1 Summary of miRNAs as biomarkers in TB

Samples	LTBI	ATB	LTBI and ATB	Ref.	Year
Whole Blood	miR-6856-3p	miR-199b-3p miR-199a-3p miR-6886-3p miR-486 miR-29 miR21 miR-30 miR-20	miR-16-5p miR-374c-5p	36	2022
Whole Blood				35	2022
Whole Blood	miR-183-5p miR-409-3p miR-4286 miR-4435 miR-629-5p miR-99b-5p piR_019675	let-7a-5p, miR-196b-5p, miR-589-5p SNORD104	piR_020490 piR_017936 piR_009059 piR_020548 piR_019912 miR-4286 miR-99b-5p SNORD104	51	2019
Serum, plasma and whole blood	miR-21-5p miR-155-5p	miR-21-5p miR-26a-5p miR-29a-3p miR-144-3p miR-146-5p miR-148b-3p miR-155-5p miR-424-5p miR-484		38	2020
Exosome		miR-425 miR-96		52	2019
Plasma		hsa-miR-223-3p has-miR-448 SAMD8_hsa_circRNA994 TWF1_hsa_circRNA9897		53	2020
Serum of HIV positive patients		hsa-miR-29b-3p hsa-miR-30c-2-3p hsa-miR-197-5p hsa-miR-340-3p hsa-miR-452-5p hsa-miR-671-3 hsa-miR-885-5p hsa-miR-941 hsa-miR-3127-5p hsa-miR-3605-5p		54	2021

Citation: Castillo-Villanueva E, Rodal AIC. Under diagnosis of tuberculosis in times of pandemic and the use of microRNAs as biomarkers of infection. *J Microbiol Exp*. 2022;10(5):156–160. DOI: 10.15406/jmen.2022.10.00368

However, so far, despite many publications in the last decade, miRNA research has not resulted in consistent or validated biomarkers for the detection of TB or TBL,[35] nor for other diseases such as cancer.[38,45-47] The question is, why is there such a wide discrepancy between the miRNAs found, and to determine this, more sample analysis and conditions are needed to determine whether or not it will be possible to translate microRNA biomarkers from the laboratory to the clinic. In the case of active and latent tuberculosis infection, as shown in Table 1, the published results have not been able to reach a consensus on which microRNAs can be used as biomarkers of MTB infection.[35] Another point to consider is that, depending on the origin of the sample obtained, it is the molecular signature that should be sought in order to be able to give an accurate result. Although there is still a long way to go to understand and characterize microRNAs as biomarkers, their use could be a powerful tool for molecular diagnosis not only for TB disease, but also for many other diseases of diverse etiologies.[44,48-50] To date, tuberculosis remains one of the major infectious diseases worldwide and that, with the increase in the number of cases, the decrease in diagnosis caused by the SARS-CoV-2 pandemic, and the increase in multidrug resistance, rapid and specific diagnostic modalities are required to achieve tuberculosis control.

Conclusion

Derived from the pandemic, there were serious disruptions in TB care and services, which have delayed progress toward achieving the global targets taken at the United Nations High Level Meeting (2018-2022) on TB treatment and prevention. The point of greatest concern is to end the TB Epidemic by 2035, however, with the under-diagnosis of TB cases resulting from the pandemic, it has become clear, that, if global actions are not resumed, with a holistic approach (social, personal and health system sector) to TB care, we will not be able to restore progress towards TB elimination.

On the other hand, several efforts are being made worldwide to find specific molecules that can be used for the molecular diagnosis of TB, as well as to generate new treatment alternatives for infected patients. In this sense, miRNAs have enormous therapeutic potential for the treatment of tuberculosis, since Mycobacterium tuberculosis regulates host defenses in order to survive and replicate by altering various signaling pathways. In recent studies, the role of miRNAs in the innate and adaptive immune response after MTB infection has been studied, and it has been reported that miRNAs are involved in the regulation of many altered cellular pathways in the immune response, through the regulation of host cell gene expression. However, as described in the review, there are several limitations associated with miRNAs as biomarker molecules, and one of these is that miRNAs are not specific to a single gene or a single disease, in that sense, autophagy, apoptosis or immune response, are common mechanisms in different inflammatory diseases, and it is for this reason that the same miRNAs can be present in different pathologies, and one of the strongest challenges is to be able to separate or discern tuberculosis disease from another disease that also presents an inflammatory picture such as COVID-19 or cancer, based only on the molecular signatures of microRNAs.

Acknowledgments

I would like to thank the Department of Microbiology and Parasitology for their support in conducting this review. To Dr. Rocío Tirado for her invaluable comments.

Conflicts of interest

The authors declare that there is no conflict of interest.

References

1. Can Sarinoglu R, Sili U, Eryuksel E, et al. Tuberculosis and COVID-19: An overlapping situation during pandemic. *J Infect Dev* Ctries. 2020;14(7):721–725.
2. WHO. Available from: Global Tuberculosis Report 2019. *HIV/AIDS Data Hub for the Asia-Pacific Region*; 2019.
3. Wang C, Horby PW, Hayden FG, et al. A novel coronavirus outbreak of global health concern. *Lancet.* 2020;395(10223):470–473.
4. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579(7798):265–269.
5. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–273.
6. *Novel Coronavirus (2019-nCoV) situation report 119*. World Health Organization; 2020.
7. Zimmer AJ, Klinton JS, Oga-Omenka C, et al. Tuberculosis in times of COVID-19. *J Epidemiol Community Health*. 2022;76(3):310–316.
8. Gonzalez-Domenech CM, Perez-Hernandez I, Gomez-Ayerbe C, et al. A Pandemic within other pandemics. When a multiple infection of a host occurs: SARS-CoV-2, HIV and mycobacterium tuberculosis. *Viruses*. 2021;13(5):931.
9. Hopewell PC, Reichman LB, Castro KG. Parallels and mutual lessons in tuberculosis and COVID-19 transmission, Prevention, and control. *Emerg Infect Dis.* 2021;27(3):681–686.
10. Hogan AB, Jewell BL, Sherrard-Smith E, et al. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. *Lancet Glob Health*. 2020;8(9):1132–1141.
11. Dass SA, Balakrishnan V, Arifin N, et al. The COVID-19/Tuberculosis syndemic and potential antibody therapy for TB based on the lessons learnt from the pandemic. *Front Immunol*. 2022;13:833715.
12. Mousquer GT, Peres A, Fiegenbaum M. Pathology of TB/COVID-19 co-Infection: The phantom menace. *Tuberculosis (Edinb)*. 2021;126:102020.
13. Khayat M, Fan H, Vali Y. COVID-19 promoting the development of active tuberculosis in a patient with latent tuberculosis infection: A case report. *Respir Med Case Rep*. 2021;32:101344.
14. Cohen A, Mathiasen VD, Schon T, et al. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. *Eur Respir J.* 2019;54(3):1900655.
15. Dye C, Williams BG. The population dynamics and control of tuberculosis. *Science.* 2010;328(5980):856–861.
16. Mirzaei R, Babakhani S, Ajorloo P, et al. The emerging role of exosomal miRNAs as a diagnostic and therapeutic biomarker in Mycobacterium tuberculosis infection. *Mol Med*. 2021;27(1):34.
17. Salud OPdl. Tuberculosis en las Américas. Informe regional 2019. In: Salud OMdl, editor. *Tuberculosis en las Américas. Informe regional 2019 - OPS/OMS*. Organización Panamericana de la Salud;2019.
18. Sánchez, HJ BD, Torres O, et al. Tuberculosis en México en tiempos de COVID-19: algunas reflexiones. *Enf Emerg*. 2021; 2021:160–165.
19. Rusen ID. Challenges in tuberculosis clinical trials in the face of the COVID-19 Pandemic: A sponsor's perspective. *Trop Med Infect Dis.* 2020;5(2):86.
20. Jeremiah C, Petersen E, Nantanda R, et al. The WHO global tuberculosis 2021 Report - not so good news and turning the tide back to end TB. *Int J Infect Dis.* 2022;S1201-9712(22):149–157.
21. Salud Sd. *Distribución de casos nuevos de enfermedad por grupos de edad*. Estados Unidos Mexicanos 2019 Población General México: SSA; 2020.

22. Machado D, Couto I, Viveiros M. Advances in the molecular diagnosis of tuberculosis: From probes to genomes. *Infect Genet Evol*. 2019;72:93–112.

23. MacLean E, Kohli M, Weber SF, et al. Advances in molecular diagnosis of tuberculosis. *J Clin Microbiol*. 2020;58(10):01582–19.

24. Secretaría (SSA) dS. Situación Epidemiológica Tuberculosis. In: Centro, (CENAPRECE) NdPPyCdE, editors. México 2020 Ciudad de México: SSA, CENAPRECE, 2021.

25. Organization WH. Global Tuberculosis Report. *Informe Mundial de Tuberculosis* 2020, OMS - OPS/OMS. Organización Panamericana de la Salud (paho.org); 2020.

26. Togun T, Kampmann B, Stoker NG, et al. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. *Ann Clin Microbiol Antimicrob*. 2020;19(1):21.

27. Mulale UK, Kashamba T, Strysko J, et al. Fatal SARS-CoV-2 and mycobacterium tuberculosis coinfection in an infant: insights from Botswana. *BMJ Case Rep*. 2021;14(4):239701.

28. Sy KTL, Haw NJL, Uy J. Previous and active tuberculosis increases risk of death and prolongs recovery in patients with COVID-19. *Infect Dis (Lond)*. 2020;52(12):902-907.

29. Tiberi S, Carvalho AC, Sulis G, et al. The cursed duet today: Tuberculosis and HIV-coinfection. *Presse Med.* 2017;46(2 Pt 2):23–39.

30. Fry SH, Barnabas SL, Cotton MF. Tuberculosis and HIV-An Update on the "Cursed Duet" in Children. *Front Pediatr*. 2019;7:159.

31. Deng Y, Duan YF, Gao SP, et al. Comparison of LAMP, GeneXpert, mycobacterial culture, smear microscopy, TSPOT.TB, TBAg/PHA ratio for diagnosis of pulmonary tuberculosis. *Curr Med Sci*. 2021;41(5):1023–1028.

32. Organization WHO meeting report of a technical expert consultation: Non-inferiority analysis of Xpert MTB/RIF ultra compared to Xpert MTB/RIF; 2017.

33. Organization WHO. *Latent tuberculosis infection: updated and consolidated guidelines for programmatic management*; 2018.

34. Carranza C, Pedraza-Sanchez S, de Oyarzabal-Mendez E, et al. Diagnosis for latent tuberculosis infection: New alternatives. *Front Immunol.* 2020;11:2006.

35. Pattnaik B, Patnaik N, Mittal S, et al. Micro RNAs as potential biomarkers in tuberculosis: A systematic review. *Noncoding RNA Res.* 2022;7(1):16–26.

36. Kim J, Park H, Park SB, et al. Identification of MicroRNAs as potential blood-based biomarkers for biagnosis and therapeutic monitoring of active tuberculosis. *Diagnostics (Basel)*. 2022;12(2):369.

37. Saliminejad K, Khorram Khorshid HR, Soleymani Fard S, et al. An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. *J Cell Physiol*. 2019;234(5):5451–5465.

38. Sinigaglia A, Peta E, Riccetti S, et al. Tuberculosis-associated MicroRNAs: From pathogenesis to disease biomarkers. *Cells*. 2020;9(10):2160.

39. Sabir N, Hussain T, Shah SZA, et al. miRNAs in Tuberculosis: New avenues for diagnosis and host-directed therapy. *Front Microbiol*. 2018;9:602.

40. Wang J, Yang K, Zhou L, et al. MicroRNA-155 promotes autophagy to eliminate intracellular mycobacteria by targeting Rheb. *PLoS Pathog*. 2013;9(10):1003697.

41. Lyu L, Zhang X, Li C, et al. Small RNA profiles of serum exosomes derived from individuals with latent and active tuberculosis. *Front Microbiol*. 2019;10:1174.

42. Liu M, Wang Z, Ren S, et al. Exosomes derived from mycobacterium tuberculosis-infected MSCs induce a pro-inflammatory response of macrophages. *Aging (Albany NY)*. 2021;13(8):11595–11609.

43. Castro-Magdonel BE, Orjuela M, Camacho J, et al. miRNome landscape analysis reveals a 30 miRNA core in retinoblastoma. *BMC Cancer.* 2017;17(1):458.

44. Zhu T, Liu H, Su L, et al. Identification of unique key miRNAs, TFs, and mRNAs in virulent MTB infection macrophages by network analysis. *Int J Mol Sci.* 2021;23(1):382.

45. Walzl G, McNerney R, du Plessis N, et al. Tuberculosis: advances and challenges in development of new diagnostics and biomarkers. *Lancet Infect Dis*. 2018;18(7):199–210.

46. Gao J, Fan YZ, Gao SS, et al. Circulating microRNAs as potential biomarkers for the diagnosis of endometrial cancer: a Meta-Analysis. *Reprod Sci*. 2022;28.

47. Xia T, Chen XY, Zhang YN. MicroRNAs as biomarkers and perspectives in the therapy of pancreatic cancer. *Mol Cell Biochem.* 2021;476(12):4191–203.

48. Alipoor SD, Adcock IM, Tabarsi P, et al. MiRNAs in tuberculosis: Their decisive role in the fate of TB. *Eur J Pharmacol.* 2020;886:173529.

49. Carranza C, Herrera MT, Guzman-Beltran S, et al. A dual marker for monitoring MDR-TB treatment: Host-derived miRNAs and M. tuberculosis-derived RNA sequences in serum. *Front Immunol*. 2021;12:760468.

50. Fayyad-Kazan M, Makki R, Skafi N, et al. Circulating miRNAs: Potential diagnostic role for coronavirus disease 2019 (COVID-19). *Infect Genet Evol*. 2021;94:105020.

51. de Araujo LS, Ribeiro-Alves M, Leal-Calvo T, et al. Reprogramming of small noncoding RNA populations in peripheral blood reveals host biomarkers for latent and active mycobacterium tuberculosis Infection. *mBio*. 2019;10(6):e01037-19.

52. Alipoor SD, Tabarsi P, Varahram M, et al. Serum exosomal miRNAs are associated with active pulmonary tuberculosis. *Dis Markers.* 2019;2019:1907426.

53. Yi XH, Zhang B, Fu YR, et al. STAT1 and its related molecules as potential biomarkers in mycobacterium tuberculosis infection. *J Cell Mol Med*. 2020;24(5):2866–2878.

54. Krishnan S, Queiroz ATL, Gupta A, et al. Integrative multi-omics reveals serum markers of tuberculosis in advanced HIV. *Front Immunol.* 2021;12:676980.