Original Article

C1q Levels: A Reliable Biomarker for Differentiating Active and Latent Tuberculosis Infection

Sepideh Darougar[1], Afshin Moniri[2], Parvaneh Baghaei[3], Esmaeil Mortaz[3,4], Makan Sadr[2], Arad Moniri[2], Majid Marjani[3], Payam Tabarsi[3]

[1]Department of Pediatrics, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, [2]Virology Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, [3]Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, [4]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: Tuberculosis (TB) poses a significant public health challenge, particularly because it can exist in an asymptomatic latent phase. Latent TB infection indicates the presence of *Mycobacterium tuberculosis* without clinical symptoms. Effectively distinguishing between active and latent TB is essential, especially in regions with high TB prevalence, as it may help reduce transmission rates. This study aims to evaluate C1q as a potential biomarker for differentiating active TB from latent forms. **Methods:** This prospective cross-sectional study was conducted from January 2017 to February 2018, involving HIV-negative adults aged 18 and older attending TB clinics. Participants were categorized based on clinical symptoms, imaging results, and laboratory tests into active or latent TB. Blood samples were collected to assess serum C1q levels, which were then compared between the two groups. **Results:** Out of 81 patients referred for TB evaluation, 38 were diagnosed with active TB. The overall median C1q level was 6.46 μg/ml (interquartile range 4.66–10). The active TB group exhibited significantly elevated C1q levels (10.21 μg/ml) compared to the latent TB group (6.03 μg/ml, $P < 0.001$). The area under the receiver operating characteristic curve for C1q in distinguishing active from latent TB was 0.74 (95% confidence interval, 0.63–0.85), with sensitivity varying between 61% and 82% at different threshold values. **Conclusions:** C1q shows potential as a reliable and easily obtainable biomarker for differentiating active TB from latent infection, demonstrating high sensitivity. These results underscore the need for further research to explore the clinical application of C1q in TB diagnostics.

Keywords: Active tuberculosis, biomarker, C1q, latent tuberculosis, tuberculosis

Submitted: 22-Aug-2024 **Revised:** 20-Oct-2024 **Accepted:** 28-Nov-2024 **Published:** 19-Dec-2024

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis,* has been a major threat to health throughout human history. TB, unlike most other bacterial infections, does not cause symptoms immediately. Approximately, 2–3 billion people in the world are estimated to be latently infected with *M. tuberculosis*.[1] Latent TB is a clinical state with immunologic evidence of TB without signs and symptoms of the disease.[2-4] However, 5%–15% of humans exposed to *M. tuberculosis*, develop the disease during their lifetime.[5] According to the World Health Organization, more than six million people are diagnosed with TB each year.[6] Discrimination of infection from disease is an issue of interest, particularly in TB-endemic areas[7] where the diagnosis and treatment for latent TB may open a window of opportunity to reduce TB prevalence.[7,8] Early detection of latent TB through screening of high-risk individuals for TB often involves tuberculin skin test (TST) and the interferon-gamma release assay (IGRA). However, false-negative results and false-positive results are always potential drawbacks, while the former may cause missed diagnoses and false assurance[9] and the latter may lead to unnecessary and sometimes harmful investigations.[10] Therefore, potential biomarkers have been identified that may discriminate active TB from latent TB and serum levels may also be considered as a prognostic marker in TB.[11-15]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/IJMY

DOI: 10.4103/ijmy.ijmy_194_24

Address for correspondence: Dr. Afshin Moniri, Masih Daneshvari Hospital, Darabad, Niavaran, Tehran, Iran.
E-mail: af_moniri@yahoo.com

ORCID:
Afshin Moniri: https://orcid.org/0000-0001-7237-8940

How to cite this article: Darougar S, Moniri A, Baghaei P, Mortaz E, Sadr M, Moniri A, *et al*. C1q levels: A reliable biomarker for differentiating active and latent tuberculosis infection. Int J Mycobacteriol 2024;13:404-9.

Complement functions as an important innate host defense system and C1q, a 480 kDa protein[16] is produced mainly by monocyte-derived cells, including macrophages and immature dendritic cells[17] and also by mast cells.[18] Macrophages are abundant in tissues and appear as the major source of C1q in blood,[19] while microbial factors and inflammatory cytokines regulate C1q production.[19] There are reports of versatile diverse noncomplement functions for C1q including modulation of dendritic cell maturation, production of pro-inflammatory cytokines, and T- and B-cell responses.[20] Maertzdorf *et al*., in 2011, reported an increase in C1q mRNA expression in patients with active TB.[21] Cai *et al*., in 2014, demonstrated the important value of C1q in the diagnosis of active human TB.[22]

Since searching for an ideal biomarker for distinguishing active TB from latent TB has become a relevant primary care issue, we believe that due to large limitations in the currently available diagnostic tools, the accurate and fast identification of patients with active TB is an essential need. In addition, the previous recent studies indicate that C1q upregulation in patients with active TB is associated with the disease and not as an intrinsic finding in these individuals and also it is not affected by Bacillus Calmette-Guérin (BCG) vaccination. Moreover, the upregulation of C1q is not a response to inflammation and it is significantly increased in patients with active TB compared to clinically relevant diseases in differential diagnosis such as sarcoidosis, leprosy, and pneumonia. In addition, it has been shown that with successful treatment of TB, C1q values return to normal levels of the control population.[23]

Therefore, the aim of this study is to investigate the role of C1q as an accurate and available screening test for the detection of active TB.

Methods

Ethical considerations

The research received approval from the Ethics Committee of the National Research Institute of TB and Lung Diseases (IR.SBMU.MSP.REC.1395.241). This ensures that the study was conducted in accordance with ethical guidelines and standards for research involving human subjects. Participant confidentiality was maintained throughout the study. Personal data were securely stored, and only anonymized data were used for analysis and reporting to protect participant identities.

Patient informed consent agreement

The study obtained informed consent from all participants prior to collecting blood samples. Participants were fully informed about the purpose of the study, procedures, potential risks, and their right to withdraw at any time without any consequences.

Type of sampling and reason of selection

This study utilized convenience sampling to select participants. Convenience sampling involves recruiting individuals who are readily available and willing to participate in the study within a specific timeframe and setting. The study was conducted at a specialized TB clinic in Dr. Masih Daneshvari Hospital where patients with active and latent TB frequently attend. This setting allowed for easy access to the target population.

Inclusion criteria

Age

Adult patients aged 18 years and older.

HIV status

Only HIV-negative patients were included to eliminate confounding factors associated with immunosuppression.

Diagnosis

Patients must have either active TB or latent TB as defined by clinical and laboratory criteria.

Clinical setting

Participants attending the TB clinic at Dr. Masih Daneshvari Hospital during the study period (January 2017 to February 2018).

Exclusion criteria

Major infections

Patients with any major infections, including HIV, that could affect immune responses were excluded.

Autoimmune diseases

Individuals diagnosed with autoimmune diseases were excluded to avoid skewing results due to altered complement levels.

Immunosuppression

Patients receiving immunosuppressive therapy or with conditions, leading to immunosuppression were not included.

Pregnancy

Pregnant women were excluded to prevent any potential risks associated with blood sampling and to control for hormonal influences on biomarker levels.

Recent tuberculosis treatment

Individuals who had received treatment for active TB within the last 6 months were excluded to ensure that C1q levels accurately reflected current disease status.

Patients

This prospective cross-sectional study was conducted from January 2017 to data locking on February 2018 at the Dr. Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, which is a tertiary center for TB and lung diseases. All HIV-negative adult patients over the age of 18 years attending TB clinics with active and latent TB were included. The patients suffering from any major infections (e.g. HIV infection), autoimmune diseases or immunosuppression were excluded from the study.

Definition of active tuberculosis and latent tuberculosis

Active TB patients were recruited based on clinical symptoms compatible with TB (including a persistent cough, fever, weight loss, decreased appetite, or hemoptysis), in addition

to positive mycobacterial direct smear or culture and positive imaging findings.[24]

We defined latent TB as positive interferon-gamma (IFN-γ) release assay in the absence of clinical, microbiological, and radiological evidence for active TB.[24]

Study design

A detailed medical history including age, sex, country of birth, and history of contacts in addition to clinical symptoms was collected from the patients and then, all the patients underwent the standardized clinical workup for TB (including physical examination, radiological assessment, sputum smear, and culture in addition to IFN-γ release assay. TST was not carried out in our patients due to its limited value in the diagnosis of active TB[24] in addition to routine BCG vaccination soon after birth. Those with latent TB were selected from individuals who were in close contact with patients with active TB at least 3 months before making a definite diagnosis of TB for the index patients. Active TB was excluded in this group of individuals with negative sputum smear and culture and normal chest X-ray. However, because of positive results in IGRA, they were identified as individuals with latent TB.

According to above-mentioned data, the patients were categorized into two major groups of latent TB and active disease. Then, all participants underwent C1q level measurement in their sera. C1q levels were compared in latent versus active TB.

Experiments

Sputum mycobacterial culture was confirmed by automated liquid culture and IFN-γ release assay was performed using QuantiFERON-TB Gold In-Tube®. Then, a 5 ml whole venous blood sample was obtained from each participant in an ethylenediaminetetraacetic acid blood collection tube for subsequent plasma separation and C1q levels (CIC-C1q, NovaTec Immunodiagnostica GmbH, Germany) in sera were measured and compared in active versus latent TB. For quantitative measurement of complement C1q concentrations in plasma, all reagents, samples, and standards were prepared as instructed. Standard, controls, and samples were added to appropriate wells and incubated at room temperature for 30 min. After a three-times wash, diluted conjugate was added to each well and incubated at room temperature again for another 30 min. After another three times wash with 300 µL diluted wash solution, 100 µL of TMB substrate was added and incubated in the dark at room temperature for 15 min. Finally, 100 µL of Stop solution was added to each well and the results (Absorbance at 450 nm) were read immediately.

Statistical analysis

Statistical evaluations were performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using the Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for nonnormally distributed data. Categorical variables were analyzed using Chi-square tests, with a $P < 0.05$ considered statistically significant.

In addition, the relationship between C1q levels and demographic factors such as age and gender was explored. The analysis revealed no significant correlation between C1q levels and gender ($P = 0.45$), suggesting that C1q concentrations are not influenced by this demographic factor in the context of TB.

Results

The study involved 81 patients suspected of having TB. Among these, 38 participants were diagnosed with active TB, while the remaining 43 were classified as having latent TB infection (LTBI). The demographic characteristics of the participants, including age and gender, were examined to ensure comparability between the two groups.

Demographic characteristics

The median age of participants in the study was 52.35 years. No significant age difference was found between the active TB group (median age: 52.5 years) and the LTBI group (median age: 57 years, $P = 0.92$). Among the total cohort, 51 individuals (63%) were male. The active TB group had a higher proportion of males (73.7%) compared to the LTBI group (53.5%). This gender distribution aligns with existing literature indicating that males are often more affected by active TB, potentially due to various social- and health-related factors [Table 1].

C1q level measurements

The primary focus of the study was to analyze serum C1q levels as a potential biomarker for differentiating between active TB and LTBI. Blood samples were collected from all participants, and serum C1q levels were quantified using a standardized immunoassay. The overall median C1q concentration across all participants was determined to be 6.46 µg/ml, with an interquartile range (IQR) of 4.66–10 µg/ml.

In the active TB cohort, the median C1q level was significantly higher, recorded at 10.21 µg/ml (IQR 8.43–12.76), compared to the LTBI group, which had a median C1q level of 6.03 µg/ml (IQR 4.50–8.21). This difference was statistically significant ($P < 0.001$), suggesting that elevated C1q levels are indicative of active TB. These results imply that C1q may reflect an immune response specifically associated with active infection rather than serving as a general inflammatory marker.

Receiver operating characteristic analysis

To further evaluate the diagnostic performance of C1q levels, receiver operating characteristic (ROC) analysis was

Table 1: Demographic of patients between case and control groups

Characteristics	Overall (*n*=81)	Case (*n*=38)	Control (*n*=43)	*P*
Age, mean±SD	52.35±17.23	52.55±15.52	52.16±18.80	0.92
Gender (male), *n* (%)	51 (63)	28 (73.7)	23 (53.5)	0.06
C1q	7.99±5.46	10.21±6.57	6.03±3.22	0.001

SD: Standard deviation

conducted. The area under the curve (AUC) for C1q levels was calculated to be 0.74 (95% confidence interval [CI], 0.63–0.85). An AUC value in this range indicates moderate diagnostic accuracy for the biomarker [Figure 1 and Table 2].

Different cutoff points for C1q levels were assessed to establish sensitivity and specificity. At a cutoff of 8 μg/ml, the sensitivity was found to be 61%, meaning that 61% of individuals with active TB had C1q levels above this threshold. The specificity at this cutoff was 75%, indicating that 75% of individuals with LTBI had C1q levels below this threshold. When the cutoff was raised to 10 μg/ml, sensitivity increased to 82%, but specificity decreased to 65%. These findings emphasize the inherent trade-off between sensitivity and specificity when selecting cutoff values for diagnostic testing [Figure 2].

Discussion

Biomarkers are potential complementary useful tools which have gained clinical value along the whole spectrum of a disease process. The changes of cytokines in the treatment of patients with TB are very important in the evaluation of pulmonary TB and can be considered as appropriate biomarkers to determine the effect of anti-TB treatment.[25] Detection of diagnostic biomarkers with high sensitivity and specificity for TB has been challenging during the past decades.[26] Since detection of infections such as TB in the early stages appears to significantly reduce the morbidity and mortality rates, we tried to investigate the role of C1q serum level as a biomarker in early distinguishing active TB from latent TB.

Cai *et al*., in 2014, investigated the role of C1q in TB and concluded that C1q correlated with active disease in human TB.[22] Lubbers *et al*. investigated C1q sera levels of patients with active and latent TB from Italy, Gambia, Korea, and South Africa in 2018.[23] C1q levels were elevated in their study in patients with active TB compared to latent TB in four independent cohorts which were consistent with our study.

Our findings were consistent with above-mentioned studies. In this study, C1q protein levels were again significantly higher in sera of patients with active TB (10.21 μg/ml) as compared to those with latent TB (6.03 μg/ml) ($P = 0.001$). Searching for a valuable biomarker for distinguishing active TB from latent TB, we assessed the sensitivity of C1q at different cut-offs. To determine the capacity of C1q to discriminate active TB from latent TB, the AUC of C1q levels for active TB versus latent TB was determined which was 0.737 with 95% CI. Reasonable results with sensitivity were achieved with ROC analysis from 61% to 82% at different cutoffs.

There are several factors making C1q as an optimal biomarker for distinguishing active TB from latent TB. C1q is stable and not sensitive to degradation.[17] It is easy to be measured in serum.[17] C1q is produced mainly by cells of monocytic origin (and not hepatocytes) and therefore reflects this arm of the immune system compared to other currently used TB biomarkers. C1q is not an acute phase reactant[17] which makes it more beneficial to be applied as a biomarker. Therefore, it seems that its concentration is not affected by inflammatory conditions. On the other hand, autoimmune diseases and inflammatory processes are mainly associated with complement consumption and therefore result in low levels of C1q. The only infectious condition reported so far with an increase in C1q concentration, is kala-azar.[27]

Table 2: Area under the curve and different cutoff of C1q for diagnosis of active tuberculosis

Test result variable	AUC	95% CI of AUC	Sensitivity (%)	Specificity (%)
C1q	0.737	0.629–0.845	68	67
C1q=5	0.617	0.495–0.740	82	42
C1q=6	0.624	0.502–0.747	74	51
C1q=6.5	0.679	0.561–0.798	68	67
C1q=7	0.675	0.556–0.794	61	74

TB: Tuberculosis, AUC: Area under the curve, CI: Confidence interval

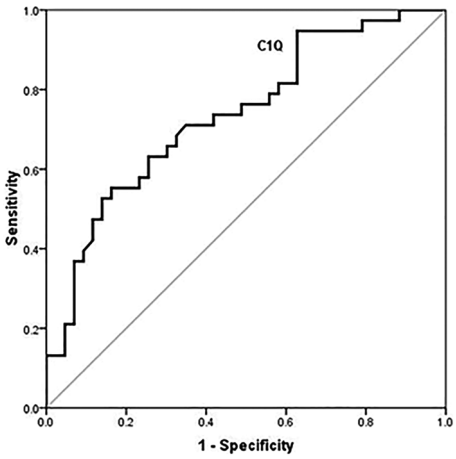

Figure 1: Sensitivity and specificity of C1Q for the diagnosis of active tuberculosis

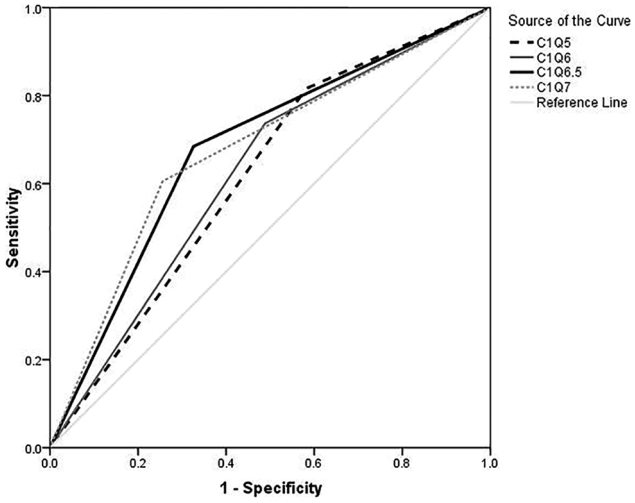

Figure 2: Sensitivity and specificity of different cutoff points of C1Q for active tuberculosis diagnosis

To conclude, C1q may act as a stable and easy-to-measure biomarker in serum to discriminate active TB from latent TB with a high sensitivity. The most significant priority of C1q as a biomarker for the detection of active TB in our study is its considerable sensitivity in different cutoff points which makes it a valuable biomarker in the diagnosis of active TB. However, future studies are needed to confirm the value of this biomarker in detection of active TB.

Conclusions

This study demonstrates that C1q levels may serve as a valuable biomarker for distinguishing between active TB and LTBI. The findings indicate that serum C1q levels are significantly higher in patients with active TB compared to those with LTBI, suggesting its potential utility in enhancing diagnostic accuracy. With sensitivity ranging from 61% to 82% and an area under the curve (AUC) of 0.74, C1q shows promise as a reliable tool for the early identification of active cases, which is crucial for the effective treatment and control of TB. Despite the study's limitations, including a small sample size and a single-center design, the results underscore the importance of exploring C1q further in diverse populations and clinical settings. Future research should aim to validate these findings and assess the practical application of C1q in routine TB screening, ultimately contributing to improved patient outcomes and public health strategies in the fight against TB.

Outcome of the study

The study successfully identified C1q as a promising biomarker for distinguishing between active TB and LTBI. Key outcomes include.

C1q level measurement

The median serum C1q level in patients with active TB was significantly higher (10.21 μg/ml) compared to those with latent TB (6.03 μg/ml), with a statistically significant difference ($P < 0.001$).

Sensitivity and specificity

The analysis demonstrated that C1q levels exhibited a sensitivity range of 61%–82% at various cutoff points. This indicates a reasonable ability to correctly identify active TB cases among the tested population.

Area under the curve

The AUC for C1q levels in differentiating active TB from LTBI was 0.74 (95% CI, 0.63–0.85). This suggests a moderate level of accuracy for C1q as a diagnostic tool.

Clinical implications

The findings highlight the potential of C1q as a stable and easily measurable biomarker that could enhance diagnostic accuracy for TB, particularly in settings where traditional diagnostic methods may yield false negatives or positives.

Overall, the study provides valuable evidence supporting the use of C1q as a biomarker in the context of TB diagnosis, emphasizing its potential to improve patient outcomes through earlier and more accurate identification of active disease.

Rationale of the study

The rationale for this study stems from several critical considerations regarding TB diagnosis and management.

Prevalence of tuberculosis

TB remains a leading cause of morbidity and mortality worldwide, with millions of new cases reported annually. Accurate diagnosis is essential for effective treatment and control of the disease, particularly in TB-endemic regions.

Challenges in diagnosis

Traditional diagnostic methods, such as the TST and IGRA, often have limitations, including false negatives and positives. These inaccuracies can lead to missed diagnoses or unnecessary treatment, complicating patient management.

Need for reliable biomarkers

There is an urgent need for reliable and easily accessible biomarkers that can differentiate between active TB and LTBI. Such biomarkers could enhance screening efforts, particularly in high-risk populations, and facilitate timely intervention.

Potential of C1q

Previous studies have suggested that C1q, a component of the complement system, may play a role in the immune response to *M. tuberculosis*. Elevated levels of C1q have been associated with active TB, indicating its potential as a biomarker for disease detection.

Public health implications

By improving the ability to accurately distinguish active TB from LTBI, the study aims to contribute to public health efforts aimed at reducing TB transmission and prevalence. Early identification of active cases can lead to prompt treatment, decreasing the risk of further infection.

Clinical relevance

The findings from this study could inform clinical practice by providing a new tool for healthcare providers in diagnosing and managing TB, ultimately improving patient outcomes.

In summary, the study is driven by the need for more effective diagnostic strategies in TB management, with the aim of leveraging C1q as a promising biomarker to enhance clinical decision-making and public health initiatives

Limitations of the study

The study involved a relatively small sample size of 81 patients. A larger cohort would enhance the statistical power and generalizability of the findings. The study was conducted at a single tertiary center, the results may not be representative of broader populations or varying demographics in different geographic locations. Differences in laboratory methods for measuring C1q levels could introduce variability.

Financial support and sponsorship
Nil.

Conflict of interest
The authors declare that the submitted work was not carried out in the presence of any personal, professional, or financial relationships that could potentially be construed as a conflict of interest.

References
1. WHO. World Health Organization. Global Tuberculosis Report, 2015. 20th ed. Geneva: WHO; 2015. Available from: https://www.who.int/publications/i/item/9789241565059. [Last accessed on 2015 Oct 27].
2. Schraufnagel DE. "Latent tuberculosis infection" is a term that should go dormant, and the significance of latent tuberculosis should be rethought. Ann Am Thorac Soc 2016;13:593-4.
3. Janagond AB, Ganesan V, Vijay Kumar GS, Ramesh A, Anand P, Mariappan M. Screening of health-care workers for latent tuberculosis infection in a tertiary care hospital. Int J Mycobacteriol 2017;6:253-7.
4. Maes R. Evaluation of the therapeutic, diagnostic, and prognostic means currently applied to counter the surge of tuberculosis. Biomed Biotechnol Res J (BBRJ) 2019;3:140-6.
5. Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect 2016;5:e10.
6. World Health Organization. Global Tuberculosis Report 2017. Geneva: World Health Organization; 20145. Available from: https://www.who.int/publications/i/item/9789241565516. [Last accessed on 2017 Jan 01].
7. Lee SH. Tuberculosis infection and latent tuberculosis. Tuberc Respir Dis (Seoul) 2016;79:201-6.
8. Güner AE, Kiziltas S, Babalik A, Sahin E, Sibel A, Safak M, *et al.* Outcomes of latent tuberculosis infection treatment in Istanbul. Int J Mycobacteriol 2022;11:442-7.
9. Fong KS, Tomford JW, Teixeira L, Fraser TG, van Duin D, Yen-Lieberman B, *et al.* Challenges of interferon-γ release assay conversions in serial testing of health-care workers in a TB control program. Chest 2012;142:55-62.
10. Slater M, Parsonnet J, Banaei N. Investigation of false-positive results given by the QuantiFERON-TB gold in-tube assay. J Clin Microbiol 2012;50:3105-7.
11. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM, *et al*. A blood RNA signature for tuberculosis disease risk: A prospective cohort study. Lancet 2016;387:2312-22.
12. Anderson ST, Kaforou M, Brent AJ, Wright VJ, Banwell CM, Chagaluka G, *et al.* Diagnosis of childhood tuberculosis and host RNA expression in Africa. N Engl J Med 2014;370:1712-23.
13. Petruccioli E, Scriba TJ, Petrone L, Hatherill M, Cirillo DM, Joosten SA, *et al.* Correlates of tuberculosis risk: Predictive biomarkers for progression to active tuberculosis. Eur Respir J 2016;48:1751-63.
14. Benachinmardi K, Sampath S, Rao M. Evaluation of a new interferon gamma release assay, in comparison to tuberculin skin tests and quantiferon tuberculosis goldplus for the detection of latent tuberculosis infection in children from a high tuberculosis burden setting. Int J Mycobacteriol 2021;10:142-8.
15. Lende TG, Waghmare P, Ambilkar AW, Kumar S. Predictive value of serum adenosine deaminase levels in prospect of tubercular infections. Biomed Biotechnol Res J (BBRJ) 2019;3:105-8.
16. Beurskens FJ, van Schaarenburg RA, Trouw LA. C1q, antibodies and anti-C1q autoantibodies. Mol Immunol 2015;68:6-13.
17. Lubbers R, van Essen MF, van Kooten C, Trouw LA. Production of complement components by cells of the immune system. Clin Exp Immunol 2017;188:183-94.
18. van Schaarenburg RA, Suurmond J, Habets KL, Brouwer MC, Wouters D, Kurreeman FA, *et al.* The production and secretion of complement component C1q by human mast cells. Mol Immunol 2016;78:164-70.
19. Lu JH, Teh BK, Wang LD, Wang YN, Tan YS, Lai MC, *et al.* The classical and regulatory functions of C1q in immunity and autoimmunity. Cell Mol Immunol 2008;5:9-21.
20. Nayak A, Pednekar L, Reid KB, Kishore U. Complement and non-complement activating functions of C1q: A prototypical innate immune molecule. Innate Immun 2012;18:350-63.
21. Maertzdorf J, Repsilber D, Parida SK, Stanley K, Roberts T, Black G, *et al.* Human gene expression profiles of susceptibility and resistance in tuberculosis. Genes Immun 2011;12:15-22.
22. Cai Y, Yang Q, Tang Y, Zhang M, Liu H, Zhang G, *et al.* Increased complement C1q level marks active disease in human tuberculosis. PLoS One 2014;9:e92340.
23. Lubbers R, Sutherland JS, Goletti D, de Paus RA, van Moorsel CH, Veltkamp M, *et al.* Complement component C1q as serum biomarker to detect active tuberculosis. Front Immunol 2018;9:2427.
24. Sandhu G, Battaglia F, Ely BK, Athanasakis D, Montoya R, Valencia T, *et al.* Discriminating active from latent tuberculosis in patients presenting to community clinics. PLoS One 2012;7:e38080.
25. Mvungi HC, Mbelele PM, Buza JJ, Mpagama SG, Sauli E. Blood cytokine responses to early secreted protein antigen-6/culture filtrate protein-10 tuberculosis antigens 2 months after antituberculosis treatment among patients with drug-susceptible pulmonary tuberculosis. Int J Mycobacteriol 2019;8:53-9.
26. Hwang H, Hwang BY, Bueno J. Biomarkers in infectious diseases. Dis Markers 2018;2018:8509127.
27. Kager PA, Hack CE, Hannema AJ, Rees PH, von dem Borne AE. High C1q levels, low C1s/C1q ratios, and high levels of circulating immune complexes in kala-azar. Clin Immunol Immunopathol 1982;23:86-93.