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The novel role of serum IL-6 and IL22 Levels as diagnostic biomarkers for the infection caused by *Mycobacterium tuberculosis*

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ABSTRACT

Interleukin-6 (IL-6) and interleukin-22 (IL-22) are major immunoregulatory cytokines that mediate inflammatory activation and affect antimicrobial defence mechanisms. This study aims to investigate the role of serum IL-6 and IL-22 levels as diagnostic biomarkers in patients with *Mycobacterium tuberculosis*. This is a hospital-based case-control study that consisted of 48 patients with *Mycobacterium tuberculosis* infection and 62 apparently healthy control subjects recruited from Al-Hussein Teaching Hospital at Karbala City, Iraq for the period between April (2025) to March (2026). Patients were grouped as active tuberculosis (n = 39) and latent tuberculosis infection (n = 9). Severe tuberculosis-related disease was also associated with significantly increased circulating levels of IL-6 and IL-22. The cytokine levels were higher in patients with active TB compared to individuals that showed latent TB infection. Both biomarkers were acceptable for their diagnostic performance as assessed by ROC curve analysis. Interleukin-6 had an area under the curve of 0.741 with sensitivity and specificity at 76.4% and 72.5%, respectively, at a cut-off value of 32.8 pg/mL. IL-22 was shown to have a slightly better diagnostic value, with an AUC of 0.768 (sensitivity 77.0%, specificity 74.2% cut-off, 46.7 pg/mL). IL-6 and IL-22 are upregulated, especially in active TB where inflammatory and immune responses predominate. Both, especially IL-22, may also be helpful as supplement biomarkers for the differentiation of tuberculosis patients from healthy subjects, and active disease from latent infection.

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Introduction

The disease has been a great public health challenge across the world and throughout its history, it continues to be one of the most infectious diseases till now all over the world especially in developing countries. It is caused by *Mycobacterium tuberculosis*, an intracellular acid-fast bacillus that primarily infects the lung but can also disseminate to extrapulmonary sites. Tuberculosis (TB) is still one of the most common causes of morbidity and mortality worldwide despite major progress in both diagnostics and new treatment

approaches(Barberis et al., 2017). Well-established early diagnostic strategies for tuberculosis and good biomarkers for disease monitoring are still urgently needed with around 10·6 million incident cases of tuberculosis and nearly 1·3 million deaths reported in 2023 alone(WHO, 2024).

Upon invasion by the pathogen, the host engages in a highly complex interaction with its immune system leading to pathogenesis of tuberculosis disease. *M. tuberculosis* bacilli are engulfed by alveolar macrophages post inhalation, where they have also been shown to survive and replicate intracellularly via a myriad of immune evasion mechanisms. T-helper (Th) lymphocyte mediated immune responses and macrophage activation pathways, which regulate granuloma formation and bacterial containment during host deficits to TB obtained from data prior to October 2023. Cytokines are a crucial component in regulating these immune responses, and modifications of the cytokine profile have been correlated (Pai et al., 2016)

While a wide variety of inflammatory cytokines have been suggested to play a role in tuberculosis immunity, interleukin-6 (IL-6) and interleukin-22 (IL-22) have recently attracted much scientific attention among others. IL-6 is a pleiotropic pro-inflammatory cytokine secreted by activated macrophages, dendritic cells, monocytes, fibroblasts and endothelial tissues in response to infection or injury. It plays roles in both innate and adaptive immune responses by eliciting acute phase reactions, supporting B-cell differentiation, T-cell activation and driving inflammatory signaling pathways(Martinez et al., 2013). IL-6 is involved in macrophage activation and modulation of granulomatous inflammation during *M. tuberculosis* infection. Serum IL-6 has been found to be elevated in patients with active TB, indicating that its quantitation may reflect inflammatory burden and disease activity(Lyu et al., 2024).

Evidence for diagnostic role of IL-6 in Tuberculosis has been shown by many authors. Gupte et al. (2021) reported markedly higher IL-6 levels in patients with active pulmonary TB compared to healthy controls, suggesting that it was able to affect host-pathogen interactions(Gupte et al., 2021). Similarly, Ahmed et al. (2023) reported elevated levels of IL-6 associated with bacterial load and radiological severity in pulmonary TB. However, IL-6 can also be produced in excessive quantity cause cytotoxicity softening tissue and contributing to CAI mechanisms during TB infection; hence their role is certainly protective but can be pathological as well(Maseko et al., 2023).

Interleukin-22 (IL-22) is another significant cytokine involved in mucosal immunity and inflammatory regulation. IL-22 is mostly produced by Th17 cells, Th22 Cells, innate lymphoid cells and natural killer (NK) cells. IL-22 is one of the few cytokines that primarily acts on non-hematopoietic epithelial cells through its ability to augment antimicrobial peptide production, promote epithelial regeneration, and reinforce barrier function(Lindahl & Olsson, 2021). Novel evidence suggests that IL-22 is also a major player in Th17-induced pulmonary resistance against *M. tuberculosis* infection via promoting epithelial barrier tightening and antimicrobial responses induction(Treerat et al., 2017).

Other studies indicated the elevated and decreased IL-22 levels in patients with tuberculosis. An investigation by Zeng et al. (2020) also showed that IL-22 is increased in the circulation of active TB patients when compared to patients with latent TB and healthy individuals, showing its potential diagnostic value(Zeng et al., 2011). Likewise, Dhiman et al. (2021) reported that IL- 22 producing T-cells were significantly increased in patients with pulmonary TB and they were correlated both to disease severity and also reported cause of inflammatory progression. These results suggest that IL-22 may represent a marker of immune activity during the host response to tuberculosis(Dhiman et al., 2009).

The evaluation of both IL-6 and IL-22 combined may give important information regarding tuberculous immunopathogenesis. IL-6 reflects systemic inflammatory activation, whereas IL-22 is related more to mucosal immunity and tissue repair mechanisms. As such, simultaneous measurement of these cytokines may potentially increase diagnostic accuracy related to active disease versus healthy states (Carabalí-Isajar et al., 2023). In addition to this, for the aforementioned reasons, cytokine-based biomarkers outcompete conventional diagnostics as potential rapid, minimally-invasive and immunologically-informative approaches to disease detection. Conventional diagnostic modality for TB, which are sputum smear microscopy, culture species, chest radiography and molecular assays like GeneXpert express has various limitations regarding sensitivity, specificity, time consuming as well as they access very limited in low resource settings (Lawn & Zumla, 2011). Thus, increasing efforts are directed toward discovery of novel immunological biomarkers that might accompany existing diagnostics and assist in early identification of disease. Conceptual basis: It is important to comprehend the immunological changes associated with TB infection in order to achieve innovative diagnostic and therapeutic methods. Determination of serum levels of IL-6 and IL-22 may help to elucidate some unknown aspects of host immune responses against *M. tuberculosis*, as well as a valuable tools for clinicians to assess disease status and progression. Thus, this study investigated the role of serum IL-6 and IL-22 levels as diagnostic biomarkers in patients with Mycobacterium tuberculosis.

Patients and Methods

Study Design and Setting

In this case–control study, data were collected from April 2025 to March 2026 at Hussein Teaching Hospital in Karbala, Iraq. As this hospital is one of the main tertiary referral centers for patients from Karbala and adjacent provinces in western Iraq, thus offering a broad spectrum of tuberculosis cases. This study was aimed to evaluate the diagnostic role of Interleukin-6 (IL-6) and interleukin-22 (IL-22) and compare the data for serum levels measured in patients' strains infected with *M. tuberculosis*.

Study Population

The study included 110 subjects, of whom 48 were patients whose tuberculosis infection was diagnosed and 62 were apparently healthy people who made the control group. The patient group was divided into active tuberculosis (active TB) and latent tuberculosis infection (LTBI) using the clinical and laboratory findings. Participants were children and adolescents aged 10mg pred a day for >2weeks/12months), recent acute infections (<1 month), previous anti-tuberculosis treatment. These criteria were used in order to reduce potential confounding factors affecting serum cytokine levels.

Clinical and Laboratory Examination

Each of the participants received a comprehensive clinical assessment conducted by specialized physicians. Clinical assessment involved medical history and physical examination to confirm respiratory symptoms, fever, weight loss, night sweats and contact with infected persons. Chest radiographs were obtained in all suspected instances. Laboratory tests included sputum smear microscopy by Ziehl–Neelsen staining and growth of *M. tuberculosis* on culture, along with IGRA for detection of latent TB.

Sample Collection and Processing

About 5 mL of venous blood was collected aseptically from each participant using plain gel tubes. Clotted serum was then centrifuged at 3000 rpm for 10 minutes. An aliquot of serum was prepared in sterile Eppendorf tubes and stored at –20°C until biochemical analyses.

Measurement of Cytokine Levels

The serum concentrations of IL-6 and IL-22 were determined using commercially available ELISA kits (Usen Life Science Inc, Wuhan, China) following the manufacturer's instructions. In brief, standards and serum samples were added to the test wells of microplate precoated with monoclonal antibodies for human IL-6 and IL-22. Incubation was followed by washing, addition of enzyme-conjugated secondary antibodies then chromogenic substrate solution. Absorbance at 450 nm was calculated with a microplate reader. To improve the precision and reproducibility of assays, all samples were analyzed twice in parallel. Each assay run contained internal quality control samples and calibration standards.

Ethical Considerations

The Ethics Committee of Hussein Teaching Hospital and the Karbala Health Directorate reviewed and approved the study protocol (approval number: KRB/ETH/2025/021). All participants or their legal guardians were provided written informed consent before enrolment. The information regarding participants was kept strictly confidential and anonymous throughout the study.

Statistical Analysis

Data were statistically analyzed by Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean $\pm$ standard deviation (SD), while categorical variables as frequencies and percentages. Serum IL-6 and IL-22 levels were compared between patients and controls by independent sample t-test. Cytokine levels between active TB, latent TB, and controls were compared by one-way analysis of variance (ANOVA) with Tukey's post hoc test if appropriate. Categorical variables were compared using Chi-square (χ^2) test. Correlations between the cytokines and clinical parameters were also analyzed. Statistical significance was defined by a p-value < 0.05 (Al-Fahham, 2018).

Results

The demographic data demonstrated that the age and sex distribution was similar for tuberculosis patients and healthy controls. The age group of 35-44 years had the highest distribution in both groups. More males than females were represented as study participants. Tobacco consumption habit was described significantly more by tuberculosis patients (43.8%) than controls (25.8%), maybe because smoking is a recognized risk factor to pulmonary infectious diseases, including tuberculosis. (Table 1).

Table 1. Distribution of age, sex and smoking habit among study subjects

Indicators		Patients (No. = 48)		Control (No. = 62)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	25-24	18	37.50	21	33.90	0.18	0.91 (NS)
	35-44	20	41.7	28	45.2		
	> 44	10	20.8	13	21		
Sex	Male	29	60.4	36	58.1	0.06	0.80 (NS)
	Female	19	39.6	26	41.9		
Smoking	Yes	21	43.8	16	25.8		0.07 (NS)
	No	27	46.2	46	74.2		

NS: Non-significant at $P > 0.05$

The demographic characteristics within the cohort in this study were comparable between patients and controls for age, sex, history of smoking (Table 1). This resembles groups reduces the impact of demographic confounders on cytokine measurements and increases the strength of the immunological conclusions. The majority of TB patients were men which was in agreement with the epidemiology trend observed in previously published literature indicating that males are more likely to be affected by TB due to occupational exposure, smoking and physiological differences impacting immunity (WHO, 2024).

The distribution of patients according to the type of TB infection, it shows that the vast majority of patients exhibited active TB (n= 39, 81.25%), while the latent TB constituted only TB (n= 9, 18.75%) (Figure 1).

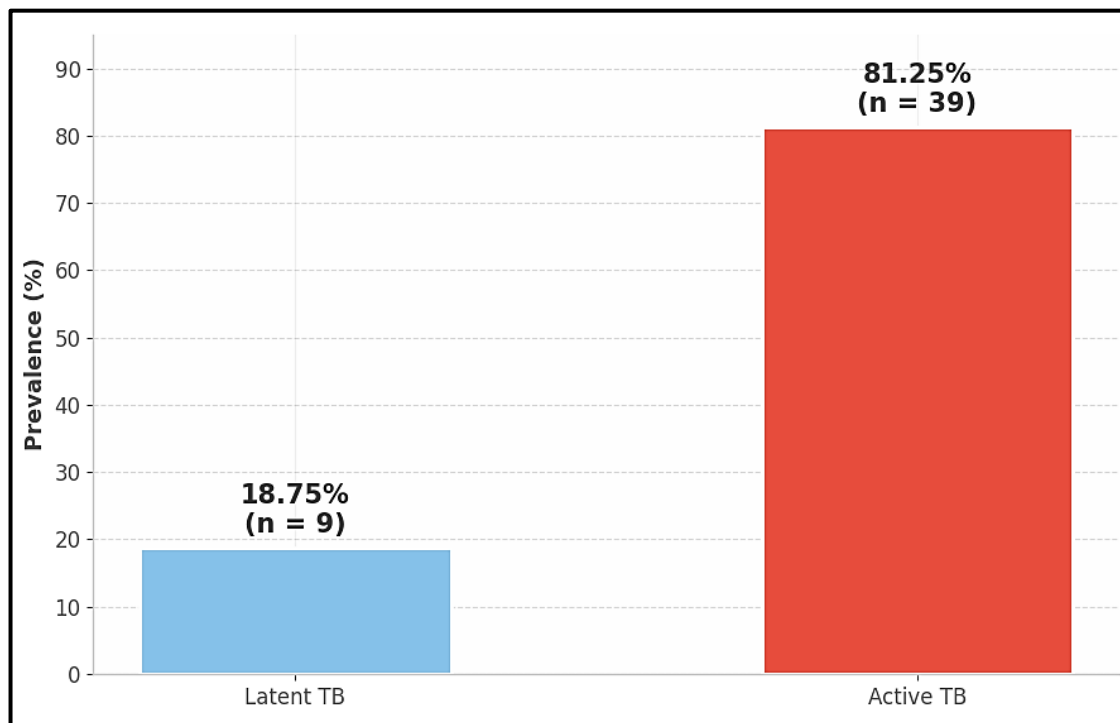


Figure 1. Distribution of patients according to the type of TB infection

Table 2 shows that IL-6 and IL-22 serum levels in patients infected with *M. tuberculosis* are higher than those of healthy control subjects. The mean serum IL-6 level (pg/mL: Mean $\pm$ SD) of tuberculosis patients approximately was 38.7 ± 8.9 pg/mL, while in the control group it was significantly lower at a mean value of 24.6 ± 6.3 pg/mL. IL-22 levels were also significantly elevated in patients (52.4 ± 11.2 pg/mL) versus controls (31.8 ± 7.5 pg/mL).

Table 2. Differences in IL-6 and IL-22 levels between patients with *Mycobacterium tuberculosis* and control participants

S:

Groups	Patient (n= 48)	Control (n=62)	T Test (P Value)
IL-6 (pg/ml) Mean ± SD	38.7 ± 8.9	24.6 ± 6.3	P < 0.03 (S)
IL-22 (pg/ml) Mean ± SD	52.4 ± 11.2	31.8 ± 7.5	P < 0.04 (S)

Significant at P<0.05

In the current study, serum IL-6 levels were also significantly higher in tuberculosis patients than in controls. IL-6 is a multifunctional pro-inflammatory cytokine produced mainly by macrophages, T lymphocytes and monocytes as part of the immune response against microbial infection. IL-6 is an important driver of the acute-phase inflammatory response and plays a key role in macrophage activation and granuloma formation during tuberculosis infection. The high IL-6 levels detected in this study could be due to residual immune activation established by *M. tuberculosis* infection and continued inflammatory tissue responses (Martinez et al., 2013; WHO, 2024).

These results correspond to a few previous studies. Sa'ad et al. However, (2024) had shown that IL-6 concentrations were statistically higher in the plasma of pulmonary TB patients compared to healthy individuals, indicating that IL-6 is an important component of host defenses and progression of disease (Sa'ad et al., 2024). Along the same lines, Hasan et al (2023) demonstrated elevated serum IL-6 levels in Iraqi patients with active tuberculosis and suggested the use of IL-6 as a biomarker for disease activity in TB. Another study by Luo et al. In patients with active TB, increased concentrations of IL-6 correlated with severe pulmonary involvement and high bacterial load (Kathamuthu et al., 2023).

Furthermore, also in the present study, levels of IL-22 were significantly higher among TB patients compared to controls. IL-22 is the member of IL-10 family cytokine and is produced mainly by Th17 cells, natural killer cells and innate lymphoid cells. IL-22 exhibits a dual role before and during TB infection, where it is known to enhance mucosal immunity, promote epithelial barrier function integrity at airways level, and modulate inflammatory responses (Dhiman et al., 2009). Higher levels of IL-22 in TB patients may suggest active protective immune pathways versus intracellular mycobacterial infection (Liu et al., 2017).

Serum concentrations of IL-6 and IL-22 in active but not latent TB disease. Model parameters for the linear regression models are presented in Table 3. Patients with active TB had a mean IL-6 of 42.5 ± 9.4 pg/mL compared to latent TB subjects (27.8 ± 5.9 pg/mL). Similarly, IL-22 concentrations were significantly elevated in active TB patients (57.6 ± 10.8 pg/mL) as compared to latent TB cases (39.3 ± 7.1 pg/mL).

Table 3. Differences in IL-6 and IL-22 levels between patients with active TB and those with latent TB

S:

Groups	Active TB (n= 39)	Latent TB (n=9)	T Test (P Value)
IL-6 (pg/ml) Mean ± SD	42.5 ± 9.4	27.8 ± 5.9	P < 0.03 (S)
IL-22 (pg/ml) Mean ± SD	57.6 ± 10.8	39.3 ± 7.1	P < 0.02 (S)

Significant at P<0.05

Results from this study are consistent with previous reports of increased IL-22 levels during the active phase of tuberculosis disease. Xu et al. in their study performed on active TB spleens, showed that IL-22 production is significantly increased and associated with disease severity (Xu et al., 2024). Likewise, Scriba et al. In line with this, IL-22 expression was found up-regulated in pulmonary TB patients and proposed a role for the cytokine in granuloma maintenance and immune regulation. Furthermore, Liu et al. (2017) highlighted that IL-22 is important for host defense by mediating antimicrobial peptide production and containment of tissue damage during ongoing infection (Liu et al., 2017).

One of the key findings from this study was that levels of IL-6 and IL-22 are significantly more elevated in patients with active TB compared to latent TB infection. This observation demonstrates that relatively stronger inflammatory and immunological activation among those with active disease as compared to latent infection (Gupta et al., 2023). In comparison, active tuberculosis contains the sustained replication of bacteria along with high levels of macrophage stimulation which then leads to up-regulated cytokine release. In contrast, the immune response to latent TB is characterized by more tightly controlled containment and lower inflammatory activity (Jafrasteh et al., 2021).

Previous studies that compared cytokine profiles of active and latent TB support these findings. It has been shown that individuals with active TB had a higher serum level of IL-6 than did latent infected individuals, readily indicates the higher systemic inflammation during active disease (Verbon et al., 1999). Similarly, previous studies have also demonstrated that elevated IL-22 concentrations are present in active TB patients and that the measurement of IL-22 may assist in their differentiation from LTBI (Dhiman et al., 2009; Jafrasteh et al., 2021; Liu et al., 2017; Treerat et al., 2017).

Table 4 ROC curve analysis of serum IL-6 and IL-22 for the diagnosis of *Mycobacterium tuberculosis* infection IL-6 showed an acceptable diagnostic performance with AUC of 0.741, a sensitivity of 76.4% and specificity of 72.5% at a cut-off value equal to ± 32.8 pg/mL. IL-22 had a slightly better discrimination (AUC, 0.768) sensitivity (77.0%) and specificity (74.2%) in differentiating active CD from IBD patients with optimal cut-off point of 46.7 pg/mL (Table 4, figure 3).

Table 4. Receiver operating characteristic (ROC) analysis of IL-6 and IL-22 for the diagnosis of *Mycobacterium tuberculosis*

Biomarker	(AUC)	p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
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IL-6	0.741	<0.001	32.8	76.4	72.5
IL-22	0.768	<0.001	46.7	77	74.2

AUC: Area Under the curve

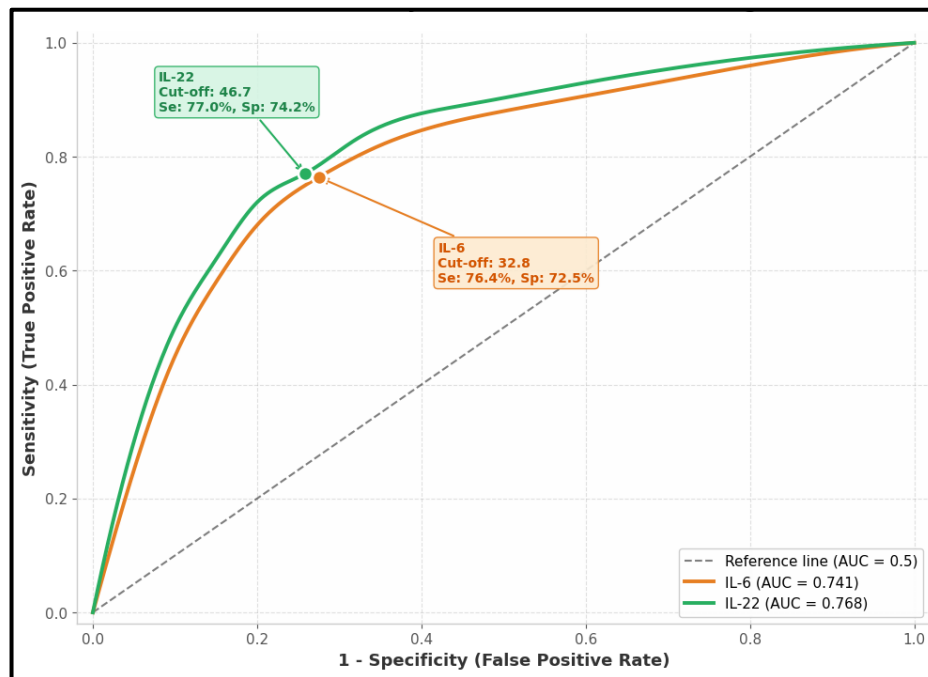


Figure 3. ROC Curve of Serum IL-6 and IL-22 Levels for diagnosing *Mycobacterium tuberculosis*

The ROC curve analysis of the present study showed that both IL-6 and IL-22 had acceptable diagnostic ability in tuberculosis infection, and compared to IL-6, our results indicated slightly better sensitivity and specificity of IL-22. The results suggest both cytokines may represent additional immunological TB biomarkers (Sinha et al., 2024). A possible explanation for the relatively higher diagnostic performance of IL-22 compared to IFN- γ is that IL-22 plays a direct role in mucosal immune defence and tissue inflammatory responses to mycobacterial infections (Cowan et al., 2012).

The potential diagnostic roles of cytokines for tuberculosis have been similarly reported in other studies. However, it has been indicated that integrations of biomarker combinations would increase the diagnostic sensitivity for active TB compared to standard test and diagnose methods based only on traditional diagnostic tests (Nogueira et al., 2022). Wan, et al (2026) showed that certain inflammatory cytokine signatures including IL-6 related pathways may aid in the rapid identification of active TB cases. Furthermore, Hur et al. One challenge in diagnosing active tuberculosis infection in patients who have had latent tuberculosis is to choose tests that result in distinguishing between the two, for which cytokine-based immunodiagnostic assays may provide additional information (Wan et al., 2026).

Thus, high levels of IL-6 and IL-22 may have biological relevance in tuberculosis with regard to macrophage activation and Th17-mediated immune responses. IL-6 is required for the differentiation of naïve T-cells into Th17 cells and IL-22 acts synergistically with several Th17 cytokines to promote antifungal defense. The ongoing increased cytokine levels may also mirror chronic inflammatory tissue damage resulting from

pulmonary TB. This suggests that the monitoring of these biomarkers may be useful indicators of disease activity and response to therapy (Ritter et al., 2020).

Although there were relevant findings in the present study, some limitations should be noted. Although there is a major effort to minimize bias in the study methods, the single-center and relatively low sample size may limit generalizability. Measurement of cytokines at one point in time may also fail to capture dynamic immunological phenomena associated with disease progression or response to treatment.

Conclusion:

Patients with *Mycobacterium tuberculosis* infection had increased serum levels of IL-6 and IL-22 compared to healthy controls. Higher concentrations of cytokines were more prominent in patients with active tuberculosis than latent infection, which correlated with adaptive and inflammatory responses during the disease course. Collectively, this study identifies two biologically important immunological functions of IL-6 and IL-22 in host defense against tuberculosis infection. It also shows both biomarkers have potential to facilitate increasing the discriminability of active vs latent TB. Additionally, IL-22 demonstrated potential in diagnosis, and it could be useful as a complementary biomarker for TB assessment. Ongoing discovery of cytokine-associated biomarkers may enable enhanced detection and improved management of tuberculosis disease in the clinical setting.

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