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Cytokine Signatures in Newly Diagnosed and Treated Pulmonary Tuberculosis Patients: Evaluation of TNF-α, IFN-γ, IL-2, and TGF-β Responses in Imo State

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Abstract **Original Research Article**

Tuberculosis (TB) remains a major global health challenge and is characterized by complex immune responses involving both pro-inflammatory and anti-inflammatory cytokines. Cytokines play crucial roles in granuloma formation, macrophage activation, bacterial containment, and tissue repair. Understanding cytokine dynamics during active disease and treatment may provide useful biomarkers for monitoring disease progression and therapeutic response.

Keywords: Pulmonary tuberculosis, Cytokines, TNF-α, IFN-γ, IL-2, TGF-β, Inflammation, Biomarkers.

Objective

To evaluate serum concentrations of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin-2 (IL-2), and transforming growth factor-beta (TGF-β) among newly diagnosed pulmonary tuberculosis patients, pulmonary tuberculosis patients receiving anti-tuberculosis therapy, and apparently healthy controls.

Introduction

Tuberculosis (TB) remains one of the leading infectious causes of death worldwide. According to the World Health Organization (WHO), approximately 10.6 million individuals developed tuberculosis in 2022, resulting in more than 1.3 million deaths globally (WHO, 2023). The disease is caused by *Mycobacterium tuberculosis*, a facultative intracellular pathogen capable of surviving within macrophages and establishing chronic infection.

Successful containment of *M. tuberculosis* depends largely on coordinated immune responses mediated by cytokines. Cytokines are soluble proteins that regulate communication between immune cells and play critical roles in

inflammation, macrophage activation, T-cell differentiation, and granuloma formation (O'Garra *et al.*, 2013).

Tumor necrosis factor-alpha (TNF-α) is a key pro-inflammatory cytokine involved in granuloma formation and maintenance. Experimental studies have demonstrated that TNF-α is essential for controlling mycobacterial growth and preventing dissemination of infection (Flynn and Chan, 2001). Similarly, interferon-gamma (IFN-γ) plays a central role in activating infected macrophages and enhancing intracellular killing of *M. tuberculosis* (Cooper *et al.*, 2007).

Interleukin-2 (IL-2) promotes T-cell proliferation, differentiation, and immune memory development. Increased IL-2 production reflects activation of adaptive cellular immunity during tuberculosis infection (Sia and Rengarajan, 2019). Conversely, transforming growth factor-beta (TGF-β) functions primarily as an immunoregulatory cytokine that suppresses excessive inflammation and promotes tissue remodeling (Letterio and Roberts, 1998).

Several studies have reported altered cytokine profiles among tuberculosis patients, suggesting that cytokines may serve as biomarkers of disease activity and treatment response (Walzl *et al.*, 2011). However, the relationships between cytokines, electrolyte homeostasis, and membrane potential remain poorly understood.

This study therefore evaluated serum TNF-α, IFN-γ, IL-2, and TGF-β concentrations among newly diagnosed pulmonary tuberculosis patients, tuberculosis patients receiving treatment, and healthy controls.

Methodology

Methods

A comparative cross-sectional study was conducted among newly diagnosed pulmonary tuberculosis patients, pulmonary tuberculosis patients on therapy, and healthy controls. Serum cytokine concentrations were determined using standard enzyme-linked immunosorbent assay (ELISA) techniques. Correlations between cytokines, electrolytes, and membrane potential were evaluated using Pearson's correlation analysis. Statistical significance was accepted at $p < 0.05$.

Study Design

A comparative cross-sectional study was conducted among pulmonary tuberculosis patients and healthy controls in Imo State.

Study Population

The study consisted of:

- Newly diagnosed pulmonary tuberculosis patients
- Pulmonary tuberculosis patients receiving anti-tuberculosis therapy
- Apparently healthy controls

Inclusion Criteria

- Confirmed pulmonary tuberculosis diagnosis.
- Patients currently receiving anti-tuberculosis treatment.
- Apparently healthy controls without evidence of tuberculosis.

Sample Collection

Five milliliters of venous blood were collected under aseptic conditions. Serum was separated and stored at appropriate temperatures until cytokine analysis.

Cytokine Analysis

Serum concentrations of the following cytokines were measured:

- TNF-α
- IFN-γ
- IL-2
- TGF-β

Measurements were performed using commercially available ELISA kits according to manufacturers' protocols.

Statistical Analysis

Data were analyzed using SPSS Version 21 software. Results were expressed as mean ± standard deviation. Group comparisons were performed using ANOVA and Student's t-test. Pearson correlation coefficients were used to assess associations among cytokines, electrolytes, and membrane potential. Statistical significance was accepted at $p < 0.05$.

Results

Serum TNF-α, IFN-γ, IL-2, and TGF-β concentrations were significantly elevated among newly diagnosed pulmonary tuberculosis patients and patients on therapy compared with healthy controls. TNF-α concentrations were significantly higher among male patients than female patients. Correlation analysis revealed a strong negative association between IFN-γ and membrane potential ($r = -0.991$, $p = 0.001$) and between IL-2 and membrane potential ($r = -0.962$, $p = 0.009$). TGF-β demonstrated a significant positive correlation with bicarbonate concentration ($r = 0.908$, $p = 0.033$).

Table 1: Cytokine Profiles Among Study Groups

Cytokine	Newly Diagnosed TB	TB on Therapy	Controls	P-value
TNF-α	Significantly Elevated	Significantly Elevated	Lowest	<0.05
IFN-γ	Significantly Elevated	Significantly Elevated	Lowest	<0.05
IL-2	Significantly Elevated	Significantly Elevated	Lowest	<0.05
TGF-β	Significantly Elevated	Significantly Elevated	Lowest	<0.05

Table 2: Correlation Between TGF-β and Electrolyte Parameter

Parameter	Correlation (r)	P-value
Sodium	0.265	0.666
Potassium	−0.751	0.144
Chloride	0.738	0.154
Bicarbonate	0.908	0.033*
Membrane Potential	−0.461	0.435

*Statistically significant.

Table 3: Correlation Between IFN-γ and Electrolyte Parameters

Parameter	Correlation (r)	P-value
Sodium	0.791	0.111
Potassium	0.224	0.718
Chloride	−0.122	0.845
Bicarbonate	0.311	0.641
Membrane Potential	−0.991	0.001*

*Statistically significant.

Table 4: Correlation Between IL-2 and Membrane Potential

Parameter	Correlation (r)	P-value
Membrane Potential	−0.962	0.009*

*Statistically significant.

Discussion

The present study demonstrated significant elevations in TNF-α, IFN-γ, IL-2, and TGF-β among pulmonary tuberculosis patients compared with healthy controls. These findings indicate robust activation of both inflammatory and regulatory immune pathways during active tuberculosis infection.

TNF-α was significantly elevated among tuberculosis patients. This finding is consistent with previous studies demonstrating the essential role of TNF-α in granuloma formation and maintenance (Flynn and Chan, 2001). TNF-α enhances macrophage activation, promotes recruitment of inflammatory cells, and contributes to containment of *M. tuberculosis* infection.

Similarly, IFN-γ concentrations were markedly increased among tuberculosis patients. IFN-γ is widely regarded as the most important protective cytokine against tuberculosis because it activates infected macrophages and stimulates intracellular killing of mycobacteria (Cooper *et al.*, 2007). Elevated IFN-γ concentrations therefore reflect active cellular immune responses against infection.

IL-2 concentrations were also significantly elevated. IL-2 plays a central role in T-cell proliferation and differentiation, facilitating expansion of antigen-specific lymphocytes and development of immunological memory (Sia and Rengarajan, 2019). Increased IL-2 production among tuberculosis patients indicates ongoing activation of adaptive immune responses.

The elevated TGF-β concentrations observed in this study likely represent regulatory mechanisms designed to limit excessive tissue damage caused by chronic inflammation. TGF-β suppresses macrophage activation and inhibits excessive cytokine production while promoting tissue repair and fibrosis (Letterio and Roberts, 1998).

An important finding of this study was the strong inverse relationship between IFN-γ and membrane potential. This observation suggests that immune activation may influence cellular electrophysiological processes through alterations in ion transport and membrane excitability. Similar mechanisms have been reported in activated immune cells undergoing cytokine-mediated signaling (Feske *et al.,* 2015).

The significant positive correlation between TGF-β and bicarbonate concentrations suggests potential interactions between immune regulation and acid-base homeostasis. This finding supports emerging evidence that metabolic pathways and immune responses are closely interconnected during chronic infectious diseases (O'Neill *et al.,* 2016).

The significant inverse association between IL-2 and membrane potential further supports the concept of immune-metabolic interactions in tuberculosis pathogenesis.

Clinical Significance

The cytokines investigated in this study may serve as useful biomarkers for:

1. Assessing disease activity.
2. Monitoring treatment response.
3. Predicting disease progression.
4. Evaluating immune competence.
5. Developing individualized treatment strategies.

Limitations

1. Cross-sectional study design.
2. Single-time-point cytokine measurements.
3. Absence of functional cytokine assays.
4. Lack of longitudinal follow-up.

Conclusion

Pulmonary tuberculosis is characterized by significant cytokine activation involving elevated TNF-α, IFN-γ, IL-2, and TGF-β concentrations. The observed relationships between cytokines, electrolyte parameters, and membrane potential suggest the existence of coordinated immune-metabolic interactions during tuberculosis infection.

These findings support the potential utility of cytokine profiling as a biomarker-based approach for disease monitoring and therapeutic evaluation.

Recommendations

1. Cytokine monitoring should be explored as an adjunctive tool for tuberculosis management.
2. Longitudinal studies should investigate cytokine dynamics throughout treatment.
3. Future studies should examine mechanistic links between cytokines and electrolyte regulation.
4. Integrated cytokine-electrolyte biomarker panels should be evaluated for prognostic applications.

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