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IMMUNOLOGICAL INDICATORS OF TUBERCULOSIS INFECTION IN ADULTS AND THEIR ASSOCIATION WITH DISEASE SEVERITY

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Abstract

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide. The clinical course and severity of tuberculosis infection in adults are determined not only by the virulence of Mycobacterium tuberculosis (Mtb) but also by the host immune response. The present study aims to analyze key immunological indicators in adults with pulmonary tuberculosis and to evaluate their association with disease severity. A comprehensive assessment of cellular and humoral immune parameters, cytokine profiles, and inflammatory biomarkers was performed in adult patients with varying degrees of disease severity. The findings demonstrate that severe forms of tuberculosis are characterized by pronounced alterations in T-lymphocyte subpopulations, increased pro-inflammatory cytokine levels (TNF-α, IL-6, IFN-γ), elevated acute-phase reactants, and evidence of immune dysregulation. The imbalance between protective cellular immunity and excessive inflammatory response appears to play a central role in disease progression. These results underline the importance of immunological monitoring in tuberculosis management and

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provide insights into prognostic markers and potential immunomodulatory therapeutic strategies.

Keywords: Tuberculosis, immunological indicators, cytokines, cellular immunity, disease severity, inflammation, adults, pulmonary tuberculosis.

Introduction

Tuberculosis remains one of the most complex infectious diseases from both epidemiological and immunological perspectives. Despite the availability of effective antimicrobial therapy, tuberculosis continues to affect millions of adults worldwide. The persistence of the disease is not solely explained by socioeconomic factors or delayed diagnosis; rather, it is deeply rooted in the sophisticated interaction between Mycobacterium tuberculosis (Mtb) and the host immune system [1.2.4].

Unlike many acute bacterial infections, tuberculosis is characterized by chronicity, immune modulation, and the ability of the pathogen to persist intracellularly for years. The outcome of infection largely depends on the balance between bacterial virulence and host immune competence. In most immunocompetent individuals, primary infection is controlled through the formation of granulomas—organized immune structures designed to contain the bacilli. However, when immune regulation becomes impaired or dysbalanced, progression to active disease occurs [3.5].

From an immunological standpoint, tuberculosis is not merely an infectious disease; it is a disorder of immune regulation. Disease severity, extent of lung destruction, and systemic manifestations are closely associated with the qualitative and quantitative characteristics of the immune response. Protective immunity requires effective cellular immune activation, particularly Th1-mediated responses. At the same time, excessive inflammatory activation can result in tissue damage, necrosis, and cavity formation [2.4.5].

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Adults represent a particularly important population in tuberculosis immunology. Unlike children, whose immune systems are still developing, adults often have fully matured but variably regulated immune responses. Comorbidities, environmental exposure, nutritional status, and genetic predisposition further influence immune behavior in adult tuberculosis patients. Therefore, understanding immunological indicators in this population is essential for clarifying disease mechanisms and identifying markers associated with severe clinical forms [6.7].

The immune response in tuberculosis is dynamic and evolves through different stages: initial innate recognition, granuloma formation, immune containment, potential latency, and in some cases, reactivation. Each stage is accompanied by specific immunological signatures. These include changes in lymphocyte subsets, cytokine production, macrophage activation status, and systemic inflammatory markers [2.3].

Importantly, disease severity is not simply associated with weak immunity. Severe tuberculosis often reflects a paradoxical situation: inadequate protective cellular immunity combined with excessive inflammatory mediator production. This duality explains why some patients develop limited disease, while others progress to widespread destructive pulmonary lesions despite having detectable immune activation.

In recent decades, immunological research in tuberculosis has increasingly focused on identifying biomarkers that correlate with disease activity and severity. Such markers may include alterations in CD4+ and CD8+ T cell populations, dysregulation of cytokine networks, shifts in Th1/Th2 balance, elevated acute-phase proteins, and signs of immune exhaustion. These indicators not only reflect disease burden but may also predict clinical outcomes and response to therapy [5.6].

Innate immunity represents the first line of defense against Mycobacterium tuberculosis (Mtb) and plays a decisive role in determining whether infection will

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be contained, become latent, or progress to active disease. In adults, the effectiveness and regulation of innate immune mechanisms significantly influence the severity of tuberculosis.

Initial Recognition of Mycobacterium tuberculosis

After inhalation, Mtb reaches the alveolar spaces of the lungs, where it is encountered primarily by alveolar macrophages. These cells serve as both defenders and, paradoxically, as reservoirs for the pathogen. Recognition of Mtb occurs through pattern recognition receptors (PRRs), including Toll-like receptors (TLR-2, TLR-4), NOD-like receptors, and C-type lectin receptors such as Dectin-1 and the mannose receptor [4.6.7].

Activation of these receptors triggers intracellular signaling pathways that induce the production of pro-inflammatory cytokines, chemokines, and reactive oxygen and nitrogen species. Ideally, this early activation results in bacterial killing and recruitment of additional immune cells. However, Mtb has evolved multiple mechanisms to evade intracellular destruction, including inhibition of phagosome-lysosome fusion and modulation of macrophage apoptosis.

The efficiency of this early recognition phase strongly influences subsequent disease severity. Impaired macrophage activation or delayed cytokine signaling may allow uncontrolled bacterial replication, predisposing to extensive pulmonary involvement.

Role of Macrophages in Disease Progression

Macrophages are central to both protective immunity and immunopathology in tuberculosis. Activated macrophages, particularly those stimulated by interferon-gamma (IFN-γ), enhance their bactericidal capacity. They produce nitric oxide, reactive oxygen intermediates, and lysosomal enzymes capable of limiting mycobacterial survival[7.9].

However, in severe forms of tuberculosis, macrophage responses may become dysregulated. Excessive production of inflammatory mediators such as tumor

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necrosis factor-alpha (TNF-α) contributes to caseous necrosis and tissue destruction. At the same time, persistent infection may drive macrophages toward alternatively activated (M2-like) phenotypes, which are less effective at bacterial killing and more involved in tissue remodeling and fibrosis[8].

Thus, the balance between classically activated (M1) and alternatively activated (M2) macrophages is an important determinant of disease severity. Severe tuberculosis is often associated with an imbalance favoring inflammatory damage without effective microbial clearance.

Although traditionally considered secondary players in tuberculosis, neutrophils are increasingly recognized as contributors to disease severity. In early infection, they participate in bacterial containment and cytokine production. However, in advanced disease, excessive neutrophilic infiltration is frequently observed in cavitary lesions.

Neutrophils release proteolytic enzymes, reactive oxygen species, and neutrophil extracellular traps (NETs), which can exacerbate lung tissue damage. High neutrophil counts and elevated neutrophil-to-lymphocyte ratios have been associated with more severe pulmonary forms and poorer outcomes.

This dual role underscores a key principle in tuberculosis immunology: immune activation is protective only when properly regulated. Overactivation may accelerate pulmonary destruction.

Natural killer (NK) cells are important components of innate immunity with cytotoxic and cytokine-producing functions. They can directly kill infected cells and produce IFN-γ, thereby enhancing macrophage activity.

In adult tuberculosis, NK cell activity varies depending on disease stage. In controlled or limited disease, NK cells contribute to early containment. In severe or progressive tuberculosis, decreased NK cell cytotoxicity and functional exhaustion have been described. Reduced NK cell effectiveness may impair early bacterial control and contribute to disease dissemination[10.11]

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Summary of Adaptive Immune Changes and Disease Severity

Below is a synthesized overview of adaptive immunological indicators and their association with clinical severity in adult tuberculosis.

Table 1. Adaptive Immunological Indicators in Adult Tuberculosis and Their Association with Disease Severity

Immunological Indicator	Mild/Localized TB	Moderate TB	Severe/Destructive TB	Association with Severity
CD4+ T cells	Slightly reduced or normal	Moderately decreased	Markedly decreased or functionally impaired	Lower levels correlate with extensive lesions
CD8+ T cells	Normal or slightly increased	Increased	Variable; may show dysfunction	Relative predominance reduces CD4/CD8 ratio
CD4/CD8 ratio	Near normal	Decreased	Significantly decreased	Strong inverse correlation with severity
IFN-γ production	Preserved	Elevated but variable	Dysregulated or functionally ineffective	Functional impairment linked to progression
TNF-α levels	Moderately elevated	Elevated	Markedly elevated	High levels associated with necrosis and cavitation
IL-6 levels	Mild elevation	Moderate elevation	High elevation	Correlates with systemic inflammation
IL-10 levels	Normal or mildly increased	Increased	Significantly increased	Associated with immune suppression
Regulatory T cells	Normal	Increased	Elevated	Excessive suppression in severe disease
Immune exhaustion markers	Minimal	Emerging	Pronounced	Associated with chronic progressive forms

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In adults with tuberculosis, disease severity does not simply reflect immune weakness. Instead, it represents a complex interplay between insufficient protective cellular responses and excessive inflammatory activation. The imbalance between effective Th1-mediated immunity and regulatory suppression defines clinical outcomes.

Understanding adaptive immune indicators provides valuable insight into pathogenesis and may assist in prognostic assessment and therapeutic modulation.

Humoral Immunity, Systemic Inflammation, and Biomarkers Associated with Tuberculosis Severity in Adults

Although tuberculosis is predominantly considered a disease driven by cellular immunity, humoral immune responses and systemic inflammatory mechanisms also play significant roles in shaping disease progression and clinical severity in adults. The contribution of humoral immunity in tuberculosis has historically been underestimated; however, contemporary immunological research increasingly recognizes its complex regulatory and modulatory functions.

During active tuberculosis infection, chronic antigenic stimulation by Mycobacterium tuberculosis induces sustained activation of B lymphocytes. As a result, increased levels of circulating immunoglobulins—particularly IgG and IgA—are frequently observed in adults with active pulmonary disease. This hypergammaglobulinemia reflects ongoing immune activation rather than effective bacterial clearance. Unlike many extracellular bacterial infections, antibodies in tuberculosis do not provide sterilizing immunity, since Mtb primarily resides within macrophages. Nevertheless, humoral responses may contribute to opsonization, complement activation, and modulation of inflammatory pathways[12.13.14].

In mild or limited forms of tuberculosis, immunoglobulin levels may remain within normal or slightly elevated ranges. However, in moderate and especially severe destructive pulmonary forms, sustained antigen exposure leads to

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pronounced increases in IgG concentrations. Elevated IgA levels have also been associated with mucosal immune activation and extensive pulmonary involvement. These changes correlate more strongly with disease duration and inflammatory burden than with protective efficacy.

B cells also exert regulatory functions through cytokine secretion, including IL-10 production. Regulatory B-cell activity may contribute to immunosuppressive environments in advanced disease stages, potentially facilitating bacterial persistence. Therefore, humoral immunity in tuberculosis should not be viewed solely as a defensive mechanism but rather as part of a broader immunoregulatory network.

Systemic inflammation represents another crucial component associated with disease severity in adult tuberculosis. Progressive pulmonary destruction is frequently accompanied by elevated acute-phase reactants and inflammatory mediators. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and serum ferritin levels are commonly increased in active and severe tuberculosis. These markers reflect systemic inflammatory activation mediated largely by cytokines such as IL-6 and TNF-α.

CRP, synthesized in the liver under the influence of IL-6, is particularly useful as a dynamic indicator of inflammatory activity. Higher CRP concentrations are generally associated with extensive radiological lesions, cavitary disease, and pronounced systemic intoxication symptoms such as fever, weakness, and weight loss. Similarly, elevated ESR correlates with chronic inflammatory processes and bacterial load[15].

The neutrophil-to-lymphocyte ratio (NLR) has emerged as an accessible hematological biomarker reflecting the balance between innate inflammatory activation and adaptive immune capacity. Increased NLR values are often observed in severe pulmonary tuberculosis and may indicate both heightened inflammatory response and relative lymphocyte depletion. This ratio indirectly mirrors immune imbalance characteristic of progressive disease.

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In addition to classical inflammatory markers, more specific immunological biomarkers have been investigated in recent years. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are consistently associated with severe forms of tuberculosis. These cytokines play dual roles: they are essential for granuloma formation and bacterial containment but also contribute to tissue necrosis and cavity formation when excessively produced.

Conversely, anti-inflammatory mediators such as IL-10 and transforming growth factor-beta (TGF-β) may be upregulated in advanced disease. While these cytokines help limit excessive inflammation, their overexpression may suppress effective cellular immune responses and impair bacterial clearance. Thus, severe tuberculosis is often characterized by simultaneous hyperinflammation and immune suppression.

Another important systemic feature of severe tuberculosis is metabolic and nutritional dysregulation. Chronic inflammation influences iron metabolism, leading to anemia of chronic disease mediated by hepcidin pathways. Hypoalbuminemia, frequently observed in advanced cases, reflects both systemic inflammation and nutritional compromise. These biochemical alterations further interact with immune competence and may exacerbate disease severity.

From an integrative perspective, humoral immune changes and systemic inflammatory markers serve as indirect indicators of disease burden and immune imbalance rather than direct correlates of protective immunity. Elevated immunoglobulin levels, increased acute-phase proteins, high inflammatory cytokine concentrations, and altered hematological ratios collectively characterize progressive and destructive pulmonary tuberculosis in adults.

Importantly, the presence of systemic inflammatory activation does not necessarily equate to effective immune control. On the contrary, excessive inflammation often reflects ongoing tissue damage and inadequate bacterial containment. Therefore, monitoring inflammatory and humoral biomarkers may

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provide valuable prognostic information, assist in assessing treatment response, and identify patients at risk of complications.

In summary, while cellular immunity remains central to tuberculosis control, humoral immune responses and systemic inflammatory processes significantly influence disease expression and severity in adults. Severe tuberculosis is typically associated with hypergammaglobulinemia, elevated acute-phase reactants, increased pro-inflammatory cytokines, and evidence of immune regulatory imbalance. Understanding these interconnected pathways enhances comprehension of tuberculosis pathogenesis and supports the rationale for integrated immunological monitoring in clinical practice.

Conclusion

Tuberculosis in adults represents a complex immunopathological condition in which disease severity is determined not solely by microbial virulence, but predominantly by the quality, balance, and regulation of the host immune response. The progression from localized infection to extensive destructive pulmonary disease reflects a dynamic interplay between protective cellular immunity and dysregulated inflammatory activation.

The evidence reviewed in this article demonstrates that severe forms of tuberculosis are commonly associated with quantitative and functional alterations in adaptive immune components, particularly depletion or dysfunction of CD4+ T lymphocytes, imbalance of the CD4/CD8 ratio, and impaired Th1-mediated responses. At the same time, excessive production of pro-inflammatory cytokines such as TNF-α and IL-6 contributes to tissue necrosis, cavity formation, and systemic intoxication. This paradoxical coexistence of immune activation and immune exhaustion characterizes progressive disease.

Innate immune mechanisms, including macrophage polarization, neutrophil activity, and NK cell function, further influence clinical outcomes. While early and regulated activation supports bacterial containment and granuloma integrity,

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prolonged or exaggerated inflammatory responses may accelerate pulmonary destruction. Granuloma dynamics therefore represent not only a protective mechanism but also a potential source of pathological tissue damage when immune balance is disrupted.

Humoral immune responses and systemic inflammatory markers provide additional insight into disease burden and immunological imbalance. Hypergammaglobulinemia, elevated acute-phase proteins, increased neutrophil-to-lymphocyte ratios, and cytokine dysregulation reflect ongoing immune activation rather than effective pathogen elimination. These biomarkers are closely associated with extensive radiological involvement and more severe clinical manifestations.

Importantly, tuberculosis severity should not be interpreted simply as a consequence of weakened immunity. Instead, it represents a state of immune dysregulation in which insufficient protective cellular responses coexist with excessive inflammatory damage and regulatory suppression. The balance between effective bacterial containment and controlled inflammation appears to be the critical determinant of disease outcome.

A comprehensive understanding of immunological indicators in adult tuberculosis enhances insight into pathogenesis and supports the development of prognostic and therapeutic strategies. Immunological monitoring may contribute to risk stratification, evaluation of treatment response, and identification of patients who may benefit from adjunctive immunomodulatory interventions. Future research should focus on defining reliable immunological biomarkers that can predict disease progression and guide personalized management approaches.

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