

## SJMLS - 9(2) - 010

**Immuno-Haematological Indices In Multi-Drug Resistant Tuberculosis: Implications For Prognosis**

Ibrahim A. Adamu<sup>1,2\*</sup>, Elujoba Samson<sup>1,3</sup>, Igbe M. kwoegbu<sup>1,4</sup>, Adepoju A. Emmanuel-Funsho<sup>1,5</sup>, Babajimi-Joseph Amarachi<sup>1,6</sup>, Muhibi A. Musa<sup>1</sup>

Department of Medical Laboratory Science, Faculty of Applied Health Sciences, Edo State University, Uzairue<sup>1</sup>, Department of Medical Laboratory Services, Ibrahim Badamasi Babangida Specialist Hospital, Minna, Niger State<sup>2</sup>, Haematology Unit, Faculty of Medical Laboratory Science, Achiever University, Ondo, Nigeria<sup>3</sup>, Defence Identification Centre, Mogadishu Cantonment, Asokoro, Abuja<sup>4</sup>, Haematology Unit, Department of Medical Laboratory Science, Elizade University; Ilara-Mokin, Ondo<sup>5</sup>, Haematology Department, Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria<sup>6</sup>

**Author for Correspondence\***: iadamu171@gmail.com/+234-806-969-1642

<https://dx.doi.org/10.4314/sokjmls.v9i2.10>

**Summary**

Multi-Drug resistant tuberculosis (MDR- TB) is a serious form of tuberculosis (TB) that is resistant to at least two of the most effective TB drugs, isoniazid (INH) and rifampicin (RMP/RIF). MDR-TB presents a significant challenge in global healthcare. Early identification of patients with poor prognosis is crucial for optimizing treatment strategies. This review explores the potential of immunohaematological indices as prognostic markers in MDR-TB. This review delves into the alterations in various blood parameters, including cell counts, inflammatory markers, and immune cell subsets, associated with MDR-TB.

**Keywords:** Monocytosis, lymphocyte, therapy, multi-drug resistant tuberculosis.

**Introduction**

Tuberculosis (TB) remains one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. In fact, globally, it has been estimated that 10.0 million people had TB in 2019, with about 1.43 million deaths. Mycobacterium tuberculosis, which mainly affects the lungs and other organs also, is the cause of TB. Drug resistance is one of the major threats to the treatment of TB. The WHO has defined multidrug-resistant TB (MDR-TB) as TB that shows resistance to isoniazid as well as rifampicin, the most effective anti-TB drugs. Pan-susceptible TB' is defined as TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that are susceptible to all first-line anti-TB drugs. In adherence to the WHO definition, other authors also opined that MDR-TB is a resistance to the two key first-line anti-TB drugs, isoniazid (INH) and rifampicin (RMP/RIF).

The term XDR-TB appeared in the literature for the first time in March 2006, It is presently defined as TB caused by strains of M. tuberculosis, which are, resistant to at least INH and RMP, plus any fluoroquinolone, and to at least one of three injectable drugs used in anti-TB treatment, capreomycin, kanamycin or amikacin.

The frequency of resistance to multiple drugs is linked to a mutation in chromosomally encoded genes. The generation of multidrug resistance in M. tuberculosis is a consequence of accumulation of mutations primarily because of inadequate or intermittent therapy or non-compliance. MDR-TB poses a severe threat due to the emergence of Mycobacterium tuberculosis strains resistant to standard first-line anti-tuberculosis drugs. Effective management requires extensive treatment regimens with increased duration and potential for severe side effects. Identifying patients at high risk of treatment failure or mortality is essential for tailoring therapeutic approaches and improving patient outcomes (Johnston *et al.*, 2012).

**THE CAUSES OF GLOBAL SPREAD OF MDR-TB****Chaotic treatment:**

Before the late 1980s, many countries were not using standard protocols for the treatment of TB and did not have systems in place to support patients. Furthermore, in many settings, TB treatment was not provided for free, contributing to poor adherence. Even today, drug-resistant TB can be created very quickly during times of socioeconomic instability if there are stockouts of anti-TB drugs or other structural weaknesses in the health care system

**Amplifier effect of short-course chemotherapy:**

Once drug resistance has been created, the DOTS strategy can paradoxically exacerbate the problem. The initial strain has polydrug resistance, but, as a result of repeated use of short-course chemotherapy, it becomes resistant to all first-line anti-TB drugs. Amplification of drug resistance patterns through repeated courses of DOTS short-course chemotherapy continues to be a major driving force of the epidemic in many parts of the world that do not have the resources to diagnose or treat drug-resistant TB correctly

**Community transmission:**

In the early 2000s, it was believed that resistance mutations conferred a loss of fitness, so the transmission of resistant strains would be self-limited (*Dye et al. 2002; Cegielski 2010*). This has not turned out to be the case. Current models indicate that in most countries, the majority of MDR-TB patients were infected initially with an MDR-TB strain, rather than slowly acquiring resistance caused by inadequate or irregular treatment.

**Facility-based transmission:**

Nosocomial transmission in busy, crowded hospitals and health centers is likely an important driver of the epidemic, especially in high HIV prevalence settings. This can result in the spread of drug-resistant strains among patients receiving therapy for drug-susceptible TB as well as to the health workers.

**IMPORTANCE OF HAEMATOLOGICAL PARAMETERS IN MDR-TB**

Haematological indices play a crucial role in the management of multi-drug resistant tuberculosis (MDR-TB) for several reasons:

**Monitoring Treatment Response:**

Haematological indices such as haemoglobin concentration, white blood cell count and platelet count can indicate how well the patient is responding to MDR-TB treatment. Changes in these indices can suggest complications or treatment efficacy.

**Identifying Adverse Effects:**

Certain drugs used to treat MDR-TB can cause haematological side effects such as anaemia, leucopaenia, or thrombocytopaenia. Monitoring these indices can help detect and manage adverse effects promptly.

**Assessing Disease Severity:**

Haematological abnormalities can be indicative of the severity of MDR-TB infection. For example, a low haemoglobin level may suggest chronicity or disseminated disease.

**Guiding Therapy Adjustments:**

If haematological indices indicate significant abnormalities, healthcare providers may need to adjust the patient's treatment regimen to minimize adverse effects while ensuring effectiveness.

**Predicting Treatment Outcomes:**

Abnormalities in haematological indices during MDR-TB treatment may correlate with treatment outcomes such as relapse or treatment failure. Close monitoring can help predict and prevent such outcomes.

Haematological indices are essential in the management of MDR-TB as they provide valuable information about treatment response, adverse effects, disease severity, and prognosis, guiding clinical decisions and improving patient outcomes (Johnston et al., 2012).

**IMMUNO-HAEMATOLOGICAL ABNORMALITIES IN MDR-TB:**

As earlier elucidated, MDR-TB infection triggers a complex immune response, reflected in alterations of various blood parameters. Some of the possible sequelae are:

**ANAEMIA:**

Anaemia is one of the most common laboratory test abnormalities seen in MDR-TB. The prevalence of anaemia in patients with diagnosis of MDR-TB ranged from 32% to 94% in studies conducted in various countries and can be associated with increased mortality and poor response to treatment. Anaemia has been considered a risk factor for the onset of infectious diseases and especially TB, as it increases individual susceptibility to such onset by reducing the immune response. Anaemia is generally present at the time of diagnosis of TB. The most frequent form is a normochromic normocytic anaemia followed by microcytic anaemia. In a previous retrospective study, authors observed that anaemia is associated with more severe forms of TB, suggesting that it could be a biomarker of the severity of the disease, with the meningeal and disseminated forms accounting for the more

severe forms of anaemia.

Many different types of blood conditions, such as anaemia, folate deficiency and sideroblastic disease, can affect TB patients. *A strong*, positive association of non-iron-deficient anaemia with TB recurrence, mortality, and HIV disease progression suggests that factors other than iron deficiency also contribute to the association of anemia with poor clinical outcomes (Minardi *et al.*, 2021).

## TOTAL & DIFFERENTIAL CELL COUNTS

### Lymphocytes:

Studies suggest a decrease in total lymphocyte counts (Gupta *et al.*, 2020), potentially indicating impaired cell-mediated immunity, crucial for TB defense.

### Neutrophils:

Elevated neutrophil counts (Farid *et al.*, 2021) are observed, suggesting a shift towards neutrophilic inflammation.

### Monocytes:

Monocytosis, an increase in monocytes, is frequently reported (Seok *et al.*, 2022) and might be linked to enhanced pro-inflammatory activity.

## INFLAMMATORY MARKERS:

### C-Reactive Protein (CRP):

Elevated CRP levels signifies systemic inflammation associated with active TB (Seok *et al.*, 2022)

### Erythrocyte Sedimentation Rate (ESR):

Increased ESR is another indicator of inflammation (Farid *et al.*, 2021)

## IMMUNE CELL SUBSETS:

### CD4+ T-lymphocytes:

Depletion of CD4+ T-cells, crucial for adaptive immunity, is observed in MDR-TB patients (Yadav *et al.*, 2021). This signifies a weakened immune response .

### Th1/Th2 Imbalance:

A shift towards a Th2 dominant immune response, characterized by increased Th2 cytokines like IL-10, is reported (Farid *et al.*, 2021). This imbalance might hinder effective anti-mycobacterial immunity.

## PROGNOSTIC SIGNIFICANCE:

Studies suggest a potential association between

abnormal immuno-haematological indices and poorer prognosis in MDR-TB:

**Lower lymphocyte counts:** Correlated with increased treatment failure and mortality rates (Gupta *et al.*, 2020).

**Elevated inflammatory markers:** Associated with a higher risk of treatment failure and death (Seok *et al.*, 2022).

**CD4+ T-lymphocyte depletion:** Linked to increased mortality and poorer treatment outcomes (Yadav *et al.*, 2021).

## LIMITATIONS

Despite promising findings, limitations exist:

**Heterogeneity of studies:** Variations in patient populations, treatment regimens, and methodological approaches call for cautions in drawing conclusions.

**Lack of standardized cut-off values:** Specific thresholds for each immuno-haematological marker to predict prognosis are yet to be established.

## FUTURE DIRECTIONS

**Standardization of assays:** Implementing standardized protocols for measuring immune cell subsets and inflammatory markers in diagnostic settings, is paramount.

**Prospective studies:** Conducting large-scale, well-designed prospective studies to validate the prognostic potential of these markers.

**Integration with clinical data:** Combining immuno-haematological data with other clinical parameters for a more robust prognostic assessment.

## CONCLUSION

Immuno-haematological indices hold promise as potential prognostic markers in MDR-TB. Abnormalities in cell counts, inflammatory markers, and immune cell subsets are associated with poorer outcomes. However, further research is warranted to establish standardized cut-offs, validate their prognostic significance in larger studies, and integrate them into comprehensive prognostic models for improved patient management in MDR-TB.

## References

Barzegari, S., Afshari, M., Movahednia, M., &

- Moosazadeh, M. (2019). Prevalence of anemia among patients with tuberculosis: A systematic review and meta-analysis. *Indian Journal of Tuberculosis*; **66(2)**: 299–307. <https://doi.org/10.1016/j.ijtb.2019.04.002>.
- Caminero, J. A., Cayla, J. A., García-García, J. M., García-Pérez, F. J., Palacios, J. J., & Ruiz-Manzano, J. (2017). Diagnosis and Treatment of Drug-Resistant Tuberculosis. *Archivos de Bronconeumología*; **53(9)**: 501–509. <https://doi.org/10.1016/j.arbr.2017.07.005>.
- Farid, S. A., El-Sayed, M. M., El-Sherbiny, M. M., & El-Sokkary, A. S. (2021). Potential role of peripheral blood immune cell subsets and inflammatory markers as predictors of treatment response and mortality in multidrug-resistant pulmonary tuberculosis. *Microbial Drug Resistance*; **27(10)**: 1516–1523.
- Gelaw, Y., Getaneh, Z., & Melku, M. (2021). Anemia as a risk factor for tuberculosis: a systematic review and meta-analysis. *Environmental Health and Preventive Medicine*; **26(1)**: 13. <https://doi.org/10.1186/s12199-020-00931-z>.
- Gupta, A., Rico-Medina, A., & Cano-Delgado, A. I. (2020). Prognostic significance of baseline blood lymphocyte count in multidrug-resistant pulmonary tuberculosis patients. *Frontiers in Public Health*; **8**: 579242.
- Johnston, J., Admon, A., Ibrahim, A., Elwood, K., Tang, P., Cook, V., & Fitzgerald, M. (2012). Long term follow-up of drug resistant and drug susceptible tuberculosis contacts in a Low incidence setting. *BMC Infectious Diseases*; **12**: <https://doi.org/10.1186/1471-2334-12-266>.
- Keshavjee, S., & Farmer, P. E. (2012). Tuberculosis, Drug Resistance, and the History of Modern Medicine. *New England Journal of Medicine*; **367(10)**:931–936. <https://doi.org/10.1056/nejmra1205429>
- Migliori, G. B., Dheda, K., Centis, R., Mwaba, P., Bates, M., O'Grady, J., Hoelscher, M., & Zumla, A. (2010). Review of multidrug-resistant and extensively drug-resistant TB: Global perspectives with a focus on sub-Saharan Africa. *Tropical Medicine and International Health*; **15(9)**: 1052–1066. <https://doi.org/10.1111/j.1365-3156.2010.02581.x>
- Minardi, M. L., Fato, I., Di Gennaro, F., Mosti, S., Mastrobattista, A., Cerva, C., Libertone, R., Saracino, A., Goletti, D., Girardi, E., Andreoni, M., Palmieri, F., & Gualano, G. (2021). Common and rare hematological manifestations and adverse drug events during treatment of active tb: A state of art. *Microorganisms*; **9(7)**: 1–15. <https://doi.org/10.3390/microorganisms9071477>
- Onyedum, C.C., Alobu, I., & Ukwaja, K. N. (2017). Prevalence of drug-resistant tuberculosis in Nigeria: A systematic review and metaanalysis. *PLoS ONE*; **12(7)**: <https://doi.org/10.1371/journal.pone.0180996>
- Palomino, J. C., & Martin, A. (2014). Drug resistance mechanisms in Mycobacterium tuberculosis. *Antibiotics*; **3(3)**: 317–340. <https://doi.org/10.3390/antibiotics3030317>.
- Seok, J. H., Lee, S., Yoo, S. G., & Seok, G. A. (2022). Clinical significance of baseline C-reactive protein and neutrophil-to-lymphocyte ratio in predicting treatment outcomes in multidrug-resistant pulmonary tuberculosis. *International Journal of Infectious Diseases*; **120**: 256–262. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10244949/>.
- Seung, K.J., Keshavjee, S., & Rich, M.L. (2015). Drug-Resistant Tuberculosis. *Cold Spring Harbor Perspectives in Medicine*, **5**.
- Yadav, R., Gupta, A., & Singh, S. K. (2021). The role of CD4 count in predicting the treatment outcome of multidrug-resistant pulmonary tuberculosis patients. *Journal of Postgraduate Medicine*; **67(2)**: 90–93. <https://stacks.cdc.gov/view/cdc/10924>.

**Citation:** Ibrahim A. Adamu, Elujoba Samson, Igbe M. kwoegbu, Adepoju A. Emmanuel-Funsho, Babajimi-Joseph Amarachi, Muhibi A. Musa. Immuno-Haematological Indices In Multi-Drug Resistant Tuberculosis: Implications For Prognosis. *Sokoto Journal of Medical Laboratory Science*; **9(2)**:77–80. <https://dx.doi.org/10.4314/sokjmls.v9i2.10>

**Copyright:** This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.