The Journal of Medical Laboratory Science & Technology South Africa. 2025;7:28-33
https://doi.org/10.36303/JMLSTSA.263

JMLSTSA
ISSN 2664 2549 EISSN 2708 3063

ORIGINAL RESEARCH

Monocyte fluorescence as a potential biomarker of tuberculosis in a HIV-prevalent setting: a hospital-based study in South Africa

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Introduction: South Africa (SA) has a high burden of tuberculosis (TB) with human immunodeficiency virus (HIV) coinfection. These patients have higher rates of sputum smear negativity, and TB diagnostics display lower sensitivity. Thus, an inexpensive, non-sputum-based TB biomarker is needed. Monocyte-derived macrophages are critical in the immune response to TB, resulting in characteristic changes in the frequency of various monocyte subsets. Sysmex haematology analysers (Sysmex, Kobe, Japan) measure monocyte activation via monocyte fluorescence (MO-Y). We evaluated MO-Y as a biomarker of TB infection in people living with HIV (PLWH). Other Sysmex extended differential parameters (EDP) and full blood count (FBC) values were assessed as secondary objectives.

Methods: The MO-Y, EDPs, and FBC values were compared among HIV seropositive and seronegative patients tested for TB in a large South African hospital.

Results: There were 120 patients (57 with TB, 63 controls) with an 84% HIV seropositivity rate. MO-Y did not differ significantly between these groups. PLWH with a CD4 count < 100 cells/µl showed significantly higher MO-Y levels, irrespective of TB status. Neutrophil surface fluorescence (NE-SFL, a marker of neutrophil activation) was considerably higher in PLWH with TB than in their HIV-negative counterparts. Possible contributing factors include more pronounced immune activation, worse illness, or concomitant bacterial infection in PLWH with TB. Among the PLWH, those with TB had significantly lower haemoglobin (Hb) levels, CD4 counts, lymphocyte counts, and mean cell volume (MCV) values. The MCV (87.4 fl cut-off value) displayed the strongest utility for discriminating between PLWH with and without TB (area under the curve [AUC] 0.78).

Conclusion: MO-Y is not an effective biomarker for TB. The MCV showed good discriminatory power between PLWH with and without TB at an 87.4 fl cut-off value.

Keywords: extended differential parameters, human immunodeficiency virus, laboratory-based study, haematology

Introduction

TB is a communicable disease caused by the microorganism *Mycobacterium tuberculosis (M. tuberculosis*).[1] Despite being a curable disease, TB is one of the top ten causes of death worldwide and is one of the top three causes of death in SA.[1,2] While great strides have been made in the diagnosis and treatment of TB in SA, it is one of six countries contributing to 60% of the global TB burden.[3] Most of TB in SA is associated with HIV infection, and SA bears the highest burden of HIV and TB coinfection worldwide.[3]

Early diagnosis is a key factor in the fight against TB, which forms the first pillar of the "End TB Strategy" by the World Health Organization (WHO).[1] The current routine laboratory methods used to diagnose TB depend upon identifying *M. tuberculosis*, most commonly from a sputum specimen.[4] Among the microbiological methods, microscopy is rapid; however, sensitivity is limited to 5 000–10 000 AFB/ml (acid-fast bacilli per millilitre) and is particularly impaired in PLWH.[5,6] In contrast, culture can require as few as 100 AFB/ml and is the gold standard of TB diagnosis; however, it requires 2–6 weeks of incubation.[5,7]

The molecular method, Xpert MTB/RIF (GXPU) (Cepheid, Sunnyvale, United States), is based on polymerase chain reaction amplification. This test has a rapid turnaround time (< 2 hours), high sensitivity and specificity (88% and 96%, respectively), and can identify *M. tuberculosis* and evidence of rifampicin resistance.[8,9] Samples can be of sputum and non-sputum origin, including but not restricted to fine needle aspirates (FNA) of serous effusions, cerebrospinal fluid (CSF), and FNA of lymph nodes.[10]

The GXPU test is not without its limitations, being relatively less sensitive in smear-negative cases and requiring a sample of adequate quality (which can be problematic in patients without a productive cough).[11,12] A robust, non-sputum-based, inexpensive TB biomarker would be valuable to complement available diagnostic test methodologies in Africa, where resources are constrained.[9]

Monocytes are the major leucocytes involved in the immune response to TB.[13] Monocytes assist in controlling TB infection and can become a reservoir for latent TB.[14] Monocytes and TB are a key area of research. Previous investigations focused on the inflammatory profile of monocytes and the polarisation

of monocytes, monocyte signal transduction, monocyte-to-lymphocyte ratios, and expression of monocyte markers in individuals with TB.[13–16] The Sysmex XT, XE, and XN haematology analysers (Sysmex, Kobe, Japan) measure the degree of MO-Y using flow cytometry whilst performing a differential white cell count, which correlates with cell activation.[17]

A recent South African study evaluating novel white cell parameters generated by the Sysmex XN-9000 haematology analyser among patients with suspected bacterial sepsis found a significant association between elevated MO-Y (as reflected by the MO-Y parameter) and a diagnosis of TB.[18] MO-Y is measured with every differential count performed on the above Sysmex analysers (a test widely performed routinely among patients with suspected infectious diseases). This parameter holds strong appeal as an inexpensive TB biomarker.

In this study, we aimed to evaluate the MO-Y parameter as a biomarker of TB infection among PLWH in the South African setting. As secondary objectives, we aimed to evaluate whether concomitant HIV infection influences the utility of MO-Y as a biomarker of TB infection and assessed the effects of TB on peripheral blood counts and other EDPs.

Methods

Sample collection

The study was performed at the Chris Hani Baragwanath Academic Hospital (CHBAH), a large academic state-sector hospital in Johannesburg, SA. Adult specimens (defined as > 18 years of age) submitted to the National Health Laboratory Service (NHLS) for TB GXPU testing were identified through a daily search of the NHLS laboratory information system (LIS). The timeframe for data access was from 1 August 2021 to 3 August 2023. The LIS was utilised to ascertain if a recent FBC and an automated differential count had been reported within the last 72 hours on the Sysmex XN-9000 haematology analyser. If the automated differential count had not been performed, refrigerated FBC samples less than 24 hours old were retrieved, and an automated differential count was performed. MO-Y, NE-SFL, and other EDPs for each differential count were obtained directly from the analyser.

The Sysmex XN-9000 measures the white cell count in the white cell chamber via impedance technology.[19] The differential count is measured in the white blood cell (WBC) differential channel using flow cytometry.[19] Cells are permeabilised, intracellular content is stained, and these are delivered to a laser point. White cell subpopulations are then identified via forward scatter (informs cell size), side scatter (informs cell complexity), and intracytoplasmic nucleic acid content.[19] MO-Y and NE-SFL are determined by measuring the fluorescent light intensity of the monocyte and neutrophil areas on the white cell differential scattergram, respectively.

Additional information obtained from the LIS included patient demographics and, if available, other laboratory results, such as HIV status, CD4 count, HIV viral load, TB culture, white cell and differential white cell counts, Hb, MCV, platelet count, bone marrow biopsy results, and the cycle threshold (CT) values on positive GXPU analysis (where lower CT values indicate a larger disease burden). As urine testing for the lipoarabinomannan (urine LAM) antigen is performed at the patient's bedside, these results were unavailable unless reported in the bone marrow biopsy report.

Since TB is far more common among PLWH, for every individual with HIV with a positive GXPU and an available FBC sample, a matching GXPU sample from an individual with HIV with a negative result and available FBC was sought. Samples were aligned based on the collection site, which included sputum, FNA, and CSF. As HIV-negative patients were scarce, all samples from HIV-negative patients with a GXPU request and an available FBC were included. Samples were consecutively included until the target sample size of approximately 100 cases in PLWH had been reached.

Samples were excluded in cases where the differential count was unavailable and the residual FBC sample was either insufficient in volume for use or was older than 24 hours. Additionally, patients with inconclusive GXPU results or those lacking an available HIV result were excluded.

Sample size calculation

The sample size was calculated to ensure adequate power for detecting a significant difference in MO-Y among PLWH with and without TB. In a prior investigation evaluating the effectiveness of EDPs in identifying bacterial sepsis, the MO-Y levels were significantly elevated in the limited cohort of patients diagnosed with TB compared with those both with and without bacterial sepsis.[18]

In this study, all patients with TB were PLWH. MO-Y did not differ significantly between TB-negative PLWH with and without bacteraemia. The mean difference in mean MO-Y between MO-Y in PLWH with TB and those without was 13.6 (E), while the standard deviation for MO-Y across all PLWH patients was 23.3 (S). Based on these results, the estimated standardised effect size is ~ 0.6 (E/S). Given an α of 0.05, 1-β of 0.80, and allowing an additional 10% for any possible errors, the calculated sample size was 50 PLWH with and without TB (total HIV + cohort of 100 patients).

Statistical analysis

TB-positive samples were defined as those with positive GXPU or TB culture results. The median MO-Y levels, other EDPs, and FBC values were compared among patients with and without TB (HIV-positive and -negative) using a Mann–Whitney U test. Statistical significance was accepted at a two-sided *p*-value of 0.05.

Receiver operating characteristic (ROC) curve analysis was performed to determine the overall performance of the relevant assay (as evidenced by the AUC). Cut-off values with the best balance between test sensitivity and specificity for identifying TB (as evidenced by a high likelihood ratio [LR] with both high sensitivity and high specificity on ROC analysis). These were selected for the EDPs and FBC parameters, which were found

Table I: FBC, differential count, and EDPs of all patients

Sample group	HIV-positive			HIV-negative		
	TB-positive (*n* = 47)	TB-negative (*n* = 54)	*p*-value*	TB-positive (*n* = 10)	TB-negative (*n* = 9)	*p*-value*
Male-to-female ratio	0.69:1	1.1:1	0.23	1:1	2:1	0.65
Age (years)						
Median	38	39.5	0.42	56	46	
IQR	30–46	31.5–49.8		24.3–70.3	33–58	0.31
CD4 count (cells/µl)						
Median	50.5	113.5				
IQR	19.3–96.3	54.5–228	0.004	-	-	
HIV viral load (log [copies/ml])						
Median	5.6	4.8				
IQR	3.0–6.0	2.9–5.5	0.25	-	-	-
Hb (g/dl)						
Median	8.4	9.6	0.016	10.35	11.20	0.65
IQR	7.2–9.9	7.7–12.8		8.83–13.10	7.28–14.23	
[13.4–17.5]†						
MCV (fl)						
Median	84.5	95.0	< 0.0001	88.95	90.20	0.35
IQR	80.1–87.8	88.0–101.8		80.40–93.35	87.25–101.6	
[83.1–101.6]†						
White cell count (× 10^9/L)						
Median	7.34	6.62	0.96	10.85	7.79	0.58
IQR	4.86–10.78	4.78–11.31		5.94–12.60	6.78–11.91	
[3.92–10.40]†						
Neutrophil count (× 10^9/L)						
Median	5.50	5.20	0.78	8.31	6.23	0.32
IQR	3.76–8.80	3.14–9.83		4.87–10.55	3.80–8.51	
[1.60–6.98]†						
Monocyte count (× 10^9/L)						
Median	0.31	0.42	0.17	0.56	0.57	0.97
IQR	0.16–0.58	0.20–0.62		0.33–0.83	0.33–0.81	
[0.30–0.80]†						
Lymphocyte count (× 10^9/L)						
Median	0.51	0.99	0.003	0.92	1.40	0.12
IQR	0.29–1.10	0.55–1.62		0.56–1.52	0.96–2.63	
[1.40–4.20]†						
Monocyte-to-lymphocyte ratio						
Median	0.49	0.45	0.11	0.54	0.46	0.66
IQR	0.31–1.07	0.27–0.62		0.37–1.04	0.27–0.82	
Platelet count (× 10^9/L)						
Median	212	232	0.36	231	275	0.85
IQR	123–297	157–341		156–378	136–491	
[171–388]†						
NE-SFL						
Median	56.10	48.65	< 0.0001	51.30	49.25	0.50
IQR	53.10–64.4	46.18–55.78		47.33–55.18	47.30–51.13	
[41.40–50.8]*						
MO-Y						
Median	117.50	113.90	0.37	108.5	109.2	0.68
IQR	106.8–125.3	106.0–121.3		104.4–115.8	107.2–113.0	
[90.0–113.8]*						

* Reference range determined at the Chris Hani Baragwanath Academic Hospital National Health Laboratory Service haematology laboratory in 40 ostensibly healthy volunteers.
† Reference range
EDP – extended differential parameter, FBC – full blood count, Hb – haemoglobin, HIV – human immunodeficiency virus, IQR – interquartile range, MCV – mean cell volume, MO-Y – monocyte fluorescence, NE-SFL – neutrophil surface fluorescent light intensity, TB – tuberculosis

to differ significantly from those of the control group. Statistical analysis was conducted utilising Prism software, version 5 (GraphPad, San Diego, United States).

Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M-210337). The committee did not mandate informed consent, as the testing was conducted on residual samples submitted for routine testing procedures. Data were recorded in an Excel spreadsheet and completely anonymised.

Results

Study population

A total of 120 samples were collected, comprising 57 samples positive for TB and 63 negative (control) samples. Of the TB-

positive patients, 53 had a positive GXPU test, and four had a negative GXPU test but with a positive TB culture. Most of the samples (81) were sputum, with the remainder including fluid/aspirates (five pleural fluid, two ascitic fluid, one pericardial fluid, four lymph node FNA, and 16 unspecified), 10 CSF samples, and a single tissue sample.

The average age of patients was 39 years, with 52.5% being female. The patients were admitted to various wards encompassing medical, surgical, and intensive care units, while two samples were collected from outpatients. The HIV seropositivity rate was 84%, with a median CD4 count of 72 cells/µl. A CD4 count could not be traced for seven patients. Relevant biometric data is shown in Table I.

Monocyte fluorescence, extended differential parameters, and blood count results

The MO-Y value did not differ significantly between the TB-positive and -negative patients, regardless of HIV status (Table I). In the analysis of the TB-positive group, a comparison of MO-Y between individuals exhibiting high CT values and those with low CT values on GXPU analysis (reflecting disease burden) revealed no statistically significant difference ($p = 0.95$). The possibility of a delay in processing affecting results was considered; however, the time to process for the samples with the lowest MO-Y value (four samples, MO-Y < 100) was not found to be significantly prolonged (median 11.7 hours). Similarly, the monocyte-to-lymphocyte ratio did not differ between the TB-positive and -negative patients, regardless of HIV status.

In PLWH, MO-Y was significantly higher in patients with a CD4 count < 100 cells/µl (median MO-Y 118.4, interquartile range [IQR] 108.8–124.2) than those with a CD4 count > 100 cells/µl (median MO-Y 108.3, IQR 102.2–121.7) ($p = 0.008$). This was found regardless of TB status, with a median MO-Y of 119.4 versus 104.7 in patients with TB and CD4 counts < 100 cells/µl and > 100 cells/µl, respectively ($p = 0.024$).

Of note, one patient with a CD4 count of 1 cell/µl had an extremely high MO-Y value (136.3) and a strong clinical suspicion of TB based on her chest radiography; however, the GXPU and TB culture were negative. A second patient with a CD4 count of 34 cells/µl and a high MO-Y value (125.3) was diagnosed with TB with difficulty, having had three negative GXPU tests and two negative TB cultures before being diagnosed with TB on a third TB culture.

The NE-SFL, Hb, CD4 counts, absolute lymphocyte counts, and MCV were significantly different in the TB-positive versus -negative groups (Table I). None of these findings were replicated in the HIV-negative group (Table I).

Receiver operating characteristic curve analysis

The results of the ROC curve analysis are presented in Table II. The MCV value showed the greatest utility in predicting TB in PLWH at an 87.4 fl cut-off value, with an AUC of 0.78. The NE-SFL also exhibited a good prediction of TB presence in these patients at a > 52.15 cut-off value. The Hb, CD4 counts, and absolute lymphocyte counts were comparatively poor biomarkers, at cut-off levels of 8.65 g/dl, 59 cells/µl, and 0.81 × 10^9/L, respectively.

Discussion

This study evaluated the application of the MO-Y value, determined by the Sysmex XN-9000 haematology analyser, to identify TB within a South African laboratory context. Our patient cohort exhibited a significant HIV seropositivity rate of 84%, underscoring the established heightened risk of TB among PLWH, along with a strong clinical suspicion for TB in this population. MO-Y did not show utility as a biomarker for TB, irrespective of HIV status. Of note, PLWH with CD4 counts < 100 cells/µl showed a higher MO-Y value than those with CD4 counts > 100 cells/µl, regardless of TB status. The raised MO-Y in this group of immunocompromised patients may be due to other opportunistic or chronic infections, resulting in monocyte activation.

Alternatively, MO-Y may still be a biomarker of TB in this subpopulation of patients since CD4 counts < 100 cells/µl have been associated with lower rates of laboratory-confirmed TB diagnoses.[20] This was illustrated by two of our patients within this group. One had a CD4 count of 34 cells/µl and underwent repeated testing, with a single positive TB culture obtained out of the six samples submitted (three GXPUs and three TB cultures). A second patient with a CD4 count of 1 cell/µl had strong radiological suspicion of TB but negative GXPU testing. This highlights that a proportion of the patients with extremely low CD4 counts, in whom TB could not be confirmed, may yet have had active TB infection and that MO-Y may still be a biomarker of TB in this subpopulation of patients.

A TB biomarker would be useful in these cases, where there is concern for smear-negative TB, resulting in reduced sensitivity

Table II: ROC curve analysis assessing the various biomarkers among PLWH with TB infection compared with those without evident TB infection

Parameter	AUC	95% CI	*p*-value for AUC	LR	Sensitivity (%)	Specificity (%)	Cut-off value	NPV (%)	PPV (%)
MO-Y	0.55	0.44 to 0.67	0.37	1.27	59.3	53.2	> 116.3	59.3	53.2
NE-SFL	0.74	0.64 to 0.84	< 0.0001	4.48	66.7	85.1	> 52.15	83.7	69.0
MCV	0.78	0.68 to 0.88	< 0.0001	3.02	75.5	75.0	< 87.35 fl	78.4	71.7
Hb	0.64	0.53 to 0.75	0.016	1.71	66.0	61.4	< 8.65 g/dl	67.3	60.0
CD4 count	0.67	0.56 to 0.79	0.004	1.86	72.0	61.4	< 59 cells/µl	67.9	65.9
Lymphocyte count	0.67	0.57 to 0.78	0.003	1.64	63.07	61.7	< 0.81 × 10^9/L	65.4	59.2

AUC – area under curve, CI – confidence interval, Hb – haemoglobin, LR – likelihood ratio, MCV – mean cell volume, MO-Y – monocyte fluorescence, NE-SFL – neutrophil surface fluorescent light intensity, NPV – negative predictive value, PLWH – people living with human immunodeficiency virus, PPV – positive predictive value, ROC – receiver operating characteristic, TB – tuberculosis

of the GXPU assay.[21] Further studies would be of interest in this group, including complete integration of urine LAM testing and microbiological, clinical, and radiological findings to better assess the value of MO-Y as an indicator of TB in PLWH with CD4 counts < 100 cells/µl.

NE-SFL was found to be significantly higher in PLWH with TB but not in the HIV-negative group. NE-SFL has previously been shown to reflect neutrophil activation and perform as a good biomarker of bacterial sepsis.[19] These findings may be due to a greater degree of general immune activation (resulting in neutrophil activation), more severe illness, or a higher rate of concomitant bacterial infection in PLWH with TB.

Among the PLWH, those with TB had significantly lower CD4 and absolute lymphocyte counts. TB infection is independently associated with lymphopaenia, owing to lymphocyte involvement in the immune response to TB and augmented by HIV coinfection.[22] This finding was observed in a previous study conducted at the NHLS at CHBAH, evaluating the changes in the FBC in PLWH and TB coinfection.[23]

Anaemia is a common haematological manifestation of TB and is suggested as the first indication of TB due to iron dysregulation.[23,24] A previous comparative cross-sectional study showed that HIV coinfection worsens the haematological abnormalities associated with pulmonary TB, including significantly lower Hb levels.[25] Our results showed that PLWH and TB coinfection had significantly lower Hb and MCV values than TB-negative controls. On ROC analysis, the parameter with the strongest diagnostic utility for discriminating PLWH with and without TB was the MCV (AUC of 0.78 at an 87.4 fl cut-off value; $p < 0.0001$).

The lower MCV values in our patient cohort are likely related to underlying anaemia of chronic disease. This hypothesis is supported by previous studies, one of which showed an improvement in both the c-reactive protein (CRP) and Hb levels during TB treatment.[26] Another supportive study investigated the haematological parameters in patients with sputum smear-positive TB. The investigators detected microcytic anaemia in patients with TB, which improved with treatment.[27] An alternative explanation for the lower MCV in patients with TB is greater antiretroviral therapy coverage in the TB-negative group. This theory is less favoured, as the HIV viral load did not differ between these groups.

Notably, there were no significant differences in any of the blood count parameters in the HIV-negative group with and without TB. This directly contrasts with several previous studies that investigated haematological manifestations of TB in patients who were not immunocompromised.[24,27–30] This is possibly explained by the smaller cohort of HIV-negative patients in this study or the fact that many previous studies used healthy controls. Yoon et al.[28] is one of the exceptions to the latter statement and used the neutrophil-to-lymphocyte ratio to differentiate pulmonary TB from community-acquired pneumonia.

Interferon-gamma release assays (IGRA) are performed on whole blood specimens and measure the cellular immune response to the *M. tuberculosis* antigen; however, these have not been used in SA's clinical setting.[31] Luo et al.[30] combined the IGRA tests and FBC results to construct a diagnostic model to differentiate between active and latent TB. The Hb, lymphocyte counts, and MCV significantly decreased in patients with active versus latent TB.[30] The investigators also postulated that routine blood testing and IGRAs in investigating immunocompromised patients may assist in identifying active TB.[30] The diagnostic utility of our significant results may be improved in combination with IGRAs; however, logistical and financial difficulties are involved in implementing this assay in the South African setting.

Study limitations

This study has several limitations. Tuberculosis diagnosis in PLWH is challenging and associated with smear-negative TB, resulting in lower rates of laboratory-confirmed TB.[21] As illustrated in one patient, diagnosis may require repeated investigation and TB cultures. Our cohort showed an 84% HIV seropositivity rate, with a median CD4 count of 72 cells/µl. This raises concerns regarding the potential for false negative results within our control group, which could significantly impact the study results. Access to bedside urine LAM test results, clinical details, and radiology findings would be beneficial in these situations.

Conclusion

MO-Y is not an effective biomarker for diagnosing TB; however, it was significantly elevated in a subgroup of PLWH with CD4 counts < 100 cells/µl. The significance of this finding is unclear and requires further study. Several additional parameters within this group exhibited a notable difference in patients with TB compared with the control group. These were Hb, CD4 counts, lymphocyte counts, and MCV. The MCV was the best discriminatory parameter for differentiating patients with and without TB at an 87.4 fl cut-off value. The diagnostic utility of these parameters may be improved by combining them with IGRAs, and further studies in this area would be of interest.

Conflict of interest

The authors declare no conflict of interest or significant financial support for this work.

Ethical approval

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M-210337).

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