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Sensitivity and specificity of the mean corpuscular volume and CD4/CD8 ratio in discriminating between rifampicin resistant and rifampicin sensitive tuberculosis

Joseph Baruch Baluku [a,b,g,*], Joseph Musaazi [c], Rose Mulwana [a], Derrick Bengo [d], Christine Sekaggya Wiltshire [c,e], Irene Andia-Biraro [e,f]

[a] Mulago National Referral Hospital, Pulmonology Division, PO Box 7051 Kampala, Uganda
[b] Makerere University Lung Institute, PO Box 7749 Kampala, Uganda
[c] Makerere University College of Health Sciences, Infectious Disease Institute, PO Box 7072 Kampala, Uganda
[d] Mulago Hospital, Department of Clinical Hematology, PO Box 7051 Kampala, Uganda
[e] Makerere University College of Health Sciences, Department of Internal Medicine, PO Box 7072 Kampala, Uganda
[f] Makerere University, Uganda Virus Research Institute Center of Excellence in Training Programme on Infections and Immunity (MUII-PLUS), PO Box 49 Entebbe, Uganda
[g] Mildmay Uganda, P.O Box 24985 Kampala, Uganda

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ABSTRACT

Background: There is need for simple, cost effective and widely available point of care tests for low level health facilities in developing countries to screen for drug resistant tuberculosis (TB) after bacteriological confirmation of TB by smear microscopy. We evaluated the sensitivity and specificity of the mean corpuscular volume (MCV) and CD4/CD8 ratio in discriminating between rifampicin resistant (RR-TB) and rifampicin sensitive (RS-TB) tuberculosis.

Methods: We performed a secondary analysis of data from a cross sectional study that enrolled adult participants with bacteriologically confirmed pulmonary TB at a national tuberculosis treatment center in Uganda. Blood samples were tested for CD4 and CD8 cell counts, HIV serology and a full hemogram. Rifampicin sensitivity and the bacillary load grade were determined by Xpert MTB/RIF®. Fifty-five participants that had RR-TB (cases) were matched with 110 participants that had RS-TB (controls) for age, sex and HIV status in a ratio of 1:2 respectively. Sensitivity (Se), specificity (Sp), area under curve (AUC) analysis and determination of optimal cut-offs were performed using receiver operating characteristic curves.

Results: Cases differed from controls with respect to residence ($p = 0.031$), bacillary load grade ($p < 0.010$) and MCV ($p = 0.021$). The Se, Sp and AUC of the MCV (cut-off of > 74.6 femtolitres (fl)) were 88.9%, 34% and 0.607 ($p = 0.021$) respectively for RR-TB. Among HIV positive participants, the respective Se, Sp and AUC of the MCV for RR-TB (cut-off of > 72.5 fl) were 97.2%, 22.2% and 0.608 ($p = 0.061$). The respective Se, Sp and AUC of the CD4/CD8 ratio (cut-off of > 0.40) were 67.3%, 50.0% and 0.559 ($p = 0.199$) on the overall and 54.1%, 71.6% and 0.628 ($p = 0.024$) among the HIV positive participants for RR-TB.

Conclusion: The MCV had a high sensitivity but very low specificity for RR-TB. The CD4/CD8 ratio had a low sensitivity and specificity for RR-TB among HIV positive individuals. The utility of either test is low due to low diagnostic accuracy.

1. Introduction

Drug resistant tuberculosis (DR-TB) is an emerging global threat to tuberculosis (TB) control and over 500,000 TB cases were estimated to be drug resistant in 2018 [1]. Notwithstanding, the World Health Organisation global TB report of 2019 indicates that<40% of these cases were notified. There are delays in DR-TB diagnosis and treatment initiation in resource limited settings due to low access to drug

* Corresponding author at: Mulago National Referral Hospital, Pulmonology Division, PO Box 7051 Kampala, Uganda.
E-mail addresses: bbjoe18@gmail.com (J. Baruch Baluku), csekaggya@idi.co.ug (C. Sekaggya Wiltshire).

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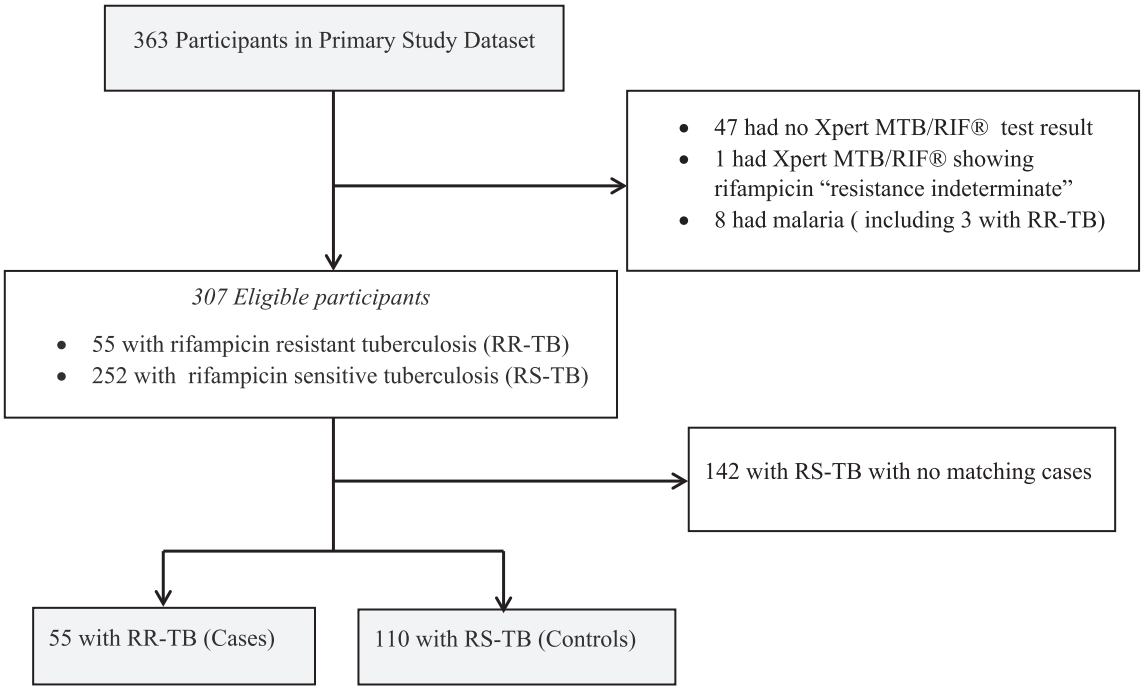

Fig. 1. Study flow chart.

susceptibility testing in low level health care facilities [2–5]. Patients that experience delays in diagnosis and treatment initiation are more likely to have poor treatment outcomes and high attrition [6–7]. Although introduction of rifampicin resistance testing via molecular methods reduces diagnosis turn-around-time and treatment initiation delays, only 35% of newly diagnosed TB patients in Africa get a rifampicin drug susceptibility test performed [8–9]. Further, in low income countries that have diagnostic sites with Xpert MTB/RIF® machines for rifampicin resistance testing, this service is generally underutilised and high costs are associated with the service in low level health care facilities [10–12]. Moreover, scaling up Xpert MBT/RIF® testing would need significant infrastructural and human resource investment that may not be afforded by resource limited countries in the short term [13]. While using non-laboratory technicians in rural areas to operate the Xpert MBT/RIF® machines is feasible, the cost-effectiveness of this intervention needs to be evaluated [14]. There is therefore a need for simple, cost effective and widely available point of care tests for low level health facilities in developing countries to screen for DR-TB, after TB confirmation by microscopy, to facilitate early referral.

The mean corpuscular volume (MCV) correlates with levels of exhaled nitric oxide [15], a marker of pulmonary inflammation that promotes increased T-helper 2 (Th2) immune responses [16]. Studies have demonstrated a local and systemic anti-inflammatory Th2 response in DR – TB that significantly differs from that observed in drug sensitive tuberculosis (DS – TB) [17–20]. However, the relationship between the MCV and drug resistant TB is unknown. Bench-top portable hemoanalyzers are available and can be used to measure red cell indices in low income settings should there be a role of the MCV and other red cell indices in the diagnosis of RR – TB [21].

The CD4/CD8 ratio has also been shown to be significantly different in patients with DR-TB when compared to patients with DS-TB [22–24]. Moreover, CD4 and CD8 testing is widely available, cost effective, acceptable and could be adapted to the existing HIV diagnosis cascade available in resource limited settings [25].

The objective of this study was to evaluate the sensitivity and specificity of the MCV and CD4/CD8 ratio in discriminating between rifampicin resistant TB (RR-TB) and rifampicin sensitive TB (RS-TB). The null hypothesis was that at an optimal cut-off, the area under the curve (AUC) of the receiver operating characteristic (ROC) curves for the aforementioned parameters would be = 0.5.

2. Materials and methods

2.1. Study population and setting

We performed a secondary analysis of data from a cross sectional study at a national tuberculosis treatment center in Uganda conducted between august 2017 and march 2018 [26]. Participants in the primary study were 18 years and older with bacteriologically confirmed TB. Blood samples were tested for HIV serology, CD4 and CD8 T-cell counts and a full hemogram. HIV testing was performed using an immunochromatographic rapid test (Alere Determine™ HIV-1/2) and a positive test was confirmed by sequential testing with another immunochromatographic test (Chembio HIV 1/2 STAT-PAK™) following the Uganda national HIV testing algorithm [27]. Determination of the CD4 and CD8 T-cell counts was performed by flow cytometry using a flow cytometer (BD FACSCalibur™) at Makerere Joint AIDS Program laboratory. Parameters of the hemogram were determined by a hemoanalyser (Sysmex® Automated hematology analyser XN series – XN 1000) at Mulago Hospital hematology laboratory. Bacillary load grade was determined by cycle threshold (Ct) values of a nucleic acid amplification test (Xpert MTB/RIF®) as follows: very low (Ct > 28), low (Ct 22–28), medium (Ct 16–22) and high (Ct < 16) [28]. In the current analysis, we included 55 participants with bacteriologically confirmed TB and rifampicin resistance reported by Xpert MTB/RIF® (Cepheid, USA) as cases. Cases were matched for age (+/- 3 years), sex and HIV status with 110 participants with bacteriologically confirmed RS-TB (controls) in a ratio of 1:2 (Cases: Controls). The effect of age, sex and HIV status on the MCV and CD4/CD8 ratio among TB patients necessitated this matching [29–30]. Eight participants with malaria infection were excluded due to the effects of malaria on the MCV and CD4/CD8 ratio [31–32].

2.2. Study measurements

Demographic and clinical characteristics, hemogram parameters, CD4 and CD8 T-cell counts, HIV serology status and bacillary load grade

Table 1
Characteristics of Study Participants.

Participant Characteristic	Cases(N = 55)	Control(N = 110)	p-value
	n (%)	n (%)	
Sex			
Male	29 (52.7)	58 (52.7)	0.999
Female	26 (47.3)	52 (47.3)	
BMI < 18.5 (kilograms/meters^2)	26 (47.3)	52 (47.3)	1.000
Age in years, median (IQR)	34 (27 – 39)	33 (27 – 39)	0.906
HIV status			
HIV positive	37 (67.3)	74 (67.3)	0.999
HIV negative	18 (32.7)	36 (32.7)	
CD4 counts (cells/mL), median (IQR)	387 (146 – 613)	281 (136 – 502)	0.110
CD4/CD8 ratio, median (IQR)	0.59 (0.28 – 1.52)	0.41 (0.21 – 1.39)	0.449
ART use			
Current ART usage	23 (41.8)	41 (37.3)	0.572
No ART usage	32 (58.2)	69 (62.7)	
ART regimen[†]			
AZT/3TC/EFV	3(13.0)	4 (9.8)	0.508
TDF/3TC/EFV	13(56.5)	29 (79.7)	
TDF/FTC/EFV	4 (17.4)	7 (17.01)	
Other ART regimen	3 (8.7)	1 (2.4)	
Bacillary load grade			
Very low	22/51 (43.1)	16/103 (15.5)	<0.001*
Low	14/51 (27.5)	26/103 (25.2)	
Medium	9/51 (17.7)	43/103 (41.8)	
High	6/51 (11.7)	18/103 (17.5)	
Residence			
Rural	27 (49.1)	35 (31.8)	0.031*
Urban	28 (50.9)	75 (68.2)	
History of TB treatment	11 (20.0)	21 (19.1)	0.889
Ever smoked in last 6 months	13 (23.6)	26 (23.6)	0.999
Ever used alcohol in last 6 months	27 (49.1)	57 (51.8)	0.741

ART- Antiretroviral therapy, AZT –Zidovudine, FTC- Emitricitabine, 3TC – Lamivudine, EFV- Efavirenz, BMI – Body mass index, IQR –interquartile range. [†]N = 23 for cases and 41 for controls respectively. *Statistically significant result.

were extracted from the primary study dataset. The study outcomes were the optimal cut offs and corresponding specificity, sensitivity and AUC for the MCV and CD4/CD8 ratio. We further performed a sub-group analysis for the sensitivity, specificity and AUC of the MCV and CD4/CD8 ratio among the HIV positive individuals. This is because of the variability of the MCV and CD4 counts among HIV/TB co-infected individuals who constituted 67% of the study population [33–35].

2.3. Statistical analysis

Data was analysed with STATA 14.2 (StataCorp, College Station, TX, USA) and MedCalc (MedCalc Software, Ostend, Belgium) was used for ROC curve analysis. Participants' characteristics were described using frequencies and percentages and compared between cases and controls using McNemar test for categorical variables. Continuous variables were summarised as medians with corresponding interquartile ranges and compared between cases and controls using Wilcoxon matched-pairs signed-ranks test. We evaluated correlation between the MCV and the variables that were significantly different between cases and controls (bacillary load and residence type) using Spearman's correlation coefficient. Further, we fitted variables that were significantly different between cases and controls in a conditional logistic regression model for factors associated with RR – TB and controlled for the haemoglobin level and body mass index (a proxy of nutritional status). For the sensitivity and specificity analysis, having RR-TB was considered the positive comparator while having RS-TB was the negative comparator. The point estimate on the ROC curve whose sensitivity and specificity gave the maximal Youden's index was considered to be the optimal cut-off and its corresponding sensitivity, specificity and AUC is reported [36]. The MCV and CD4/CD8 ratio were considered to have discriminating ability between RR-TB and RS-TB if the AUC was significantly different from the null value of 0.5 (null: AUC = 0.5). Statistical significance was set at $p \leq 0.05$ at the 95% confidence interval. Confidence intervals for sensitivity and specificity were obtained using bootstrap method.

Table 2
Comparison of hemogram parameters between cases and controls.

Hemogram parameter	CasesMedian (IQR)	ControlMedian (IQR)	P-value
MCV(fl)	82.65 (76.5 – 93.80)	81.55 (71.50 – 88.20)	0.021[Ψ]
MPV (fl)	9.50 (8.90 – 10.20)	9.40 (8.60 – 10.10)	0.271
MCH (pg)	27.15 (24.10 – 30.80)	26.20 (24.10 – 29.40)	0.184
PDW (fl)	9.80 (8.90 – 10.90)	9.60 (8.60 – 12.20)	0.951
White cell count [ϕ]	5.55 (4.38 – 7.12)	5.82 (4.28 – 7.30)	0.141
Neutrophil count [ϕ]	3.06 (1.74 – 4.98)	3.81 (2.55 – 5.36)	0.567
Lymphocyte count [ϕ]	1.27 (0.95 – 1.68)	1.22 (0.68 – 1.56)	0.261
Monocyte count [ϕ]	0.44 (0.38 – 0.65)	0.45 (0.34 – 0.71)	0.516
Eosinophil count [ϕ]	0.05 (0.01 – 0.21)	0.05 (0.01 – 0.11)	0.100
Basophil count [ϕ]	0.03 (0.01 – 0.04)	0.02 (0.01 – 0.05)	0.705
RBC count[β]	4.44 (3.52 – 5.10)	4.38 (3.45 – 5.28)	0.829
Platelet count [ϕ]	304 (240 – 387)	296 (211 – 413)	0.697
Hematocrit (%)	37.20 (32.7 – 42.0)	35.10 (28.6 – 41.6)	0.739
Hemoglobin (g/dl)	12.35 (9.90 – 14.10)	11.65 (9.40 – 13.50)	0.265
PMR	621 (416 – 900)	624 (473 – 1017)	0.962
NLR	2.43 (1.67 – 5.34)	3.06 (2.38 – 5.52)	0.536
PLR	243 (154 – 459)	265 (198 – 402)	0.522
LMR	2.97 (1.63 – 3.91)	2.47 (1.56 – 3.21)	0.127
WNR	1.63 (1.29 – 1.95)	1.47 (1.31 – 1.65)	0.091

[Ψ]Statistically significant result.
MCV-Mean corpuscular volume, MPV- Mean platelet volume, MCH –Mean corpuscular haemoglobin, PDW – platelet width distribution, RBC –red blood cell, PMR –platelet/monocyte ratio, NLR- neutrophil/lymphocyte ratio, PLR-platelet/lymphocyte ratio, LMR –lymphocyte/monocyte ratio, WNR –white cell/neutrophil ratio, [ϕ]X 10^3per mictolitre, [β]X 10^6 per microliter, g/dl- grams per decilitre, pg- picogram, fl- femtolitres.

2.4. Ethical approval and consent to participate

Study participants provided written informed consent to participate in the primary study that included consent for secondary analyses. The study was approved by the Department of Internal Medicine Scientific Review Committee (SRC) and the School of Medicine Research and Ethics Committee of Makerere University College of Health Sciences.

3. Results

From the primary study dataset, 363 participants were screened for eligibility for this analysis. Fig. 1 shows the study flow.

Table 3
Factors associated with RR - TB.

Characteristic	Adjusted odds ratio (95%confidence interval)	p- value
Mean Corpuscular Volume	1.03 (0.99 – 1.08)	0.132
Bacillary load		
Very low/low	7.47 (2.3 – 24.08)	0.001*
Medium/High	Ref	
Residence		
Rural	2.97 (0.99 – 8.90)	0.052
Urban	Ref	
Body mass index	1.07 (0.94 – 1.22)	0.287
Haemoglobin level	0.93 (0.76 – 1.12)	0.437

*Statistically significant result.

Table 4
Sensitivity, Specificity and AUC of the MCV, CD4/CD8 ratio, and other hemogram parameters.

Parameter	Optimal cut-off	Se (%) (95% CI)	Sp(%) (95% CI)	AUC	AUCp-value
CD4/CD8 ratio	>0.40	67.3 (53.3–79.3)	50.0 (40.3–59.7)	0.559	0.199
MCV (femtolitres, fl)	>74.60	88.9 (77.4–95.8)	34.0 (25.0–43.8)	0.607	0.021*
MPV (fl)	>8.70	83.3 (70.7–92.1)	29.1 (20.6–38.9)	0.543	0.362
MCH (picograms)	>29.8	31.5 (19.5–45.6)	82.1 (73.4–88.8)	0551	0.303
PDW (fl)	>10.6	27.8 (16.5–41.6)	60.2 (50.1–69.7)	0511	0.824
CD4 count (cells/ml)	>302	60.0 (45.9–73.0)	55.5 (45.7–64.9)	0.576	0.105
CD8 count (cell/ml)	>538	47.3 (33.7–61.2)	65.5 (55.8–74.3)	0.542	0.386
White cell count$^{\Phi}$	≤5.24	48.2 (34.3–62.2)	61.0 (50.9–70.3)	0.517	0.723
Neutrophil count$^{\Phi}$	≤3.33	59.4 (40.6–76.3)	60.8 (49.1–71.6)	0.598	0.117
Lymphocyte count$^{\Phi}$	>1.13	65.6 (46.8–81.4)	45.6 (34.3–57.2)	0.554	0.389
Monocyte count$^{\Phi}$	≤0.36	21.9 (9.3–40.0)	67.1 (55.6–77.3)	0.510	0.865
Eosinophil count$^{\Phi}$	>0.17	28.1 (13.7–46.7)	84.8 (75.0–91.9)	0.511	0.858
Basophil count$^{\Phi}$	≤0.04	81.3 (63.6 – 92.8)	26.6 (17.3–37.7)	0.510	0.860
RBC count$^{\beta}$	≤5.22	81.5 (68.6–90.7)	29.3 (20.8–38.9)	0.503	0.946
Platelet count$^{\Phi}$	>224	79.6 (66.5–89.4)	29.5 (21.0–39.2)	0.520	0.674
Hematocrit (%)	>33.6	72.2 (58.4–83.5)	42.5 (32.9–52.4)	0.558	0.219
Hemoglobin (g/dl)	>12.6	46.3 (32.6–60.4)	67.9 (58.2–76.7)	0.554	0.272
PMR	≤707.7	61.3 (42.2–78.2)	44.3 (33.1–55.9)	0.528	0.222
NLR	≤2.26	50.0 (31.9–68.1)	79.8 (69.2–88.0)	0.608	0.102
PLR	≤174.43	34.4 (18.6–53.2)	83.5 (73.5–90.9)	0.536	0.590
LMR	>2.82	51.6 (33.1–69.8)	64.6 (53.0–75.0)	0.574	0.259
WNR	>1.56	59.4 (40.6–76.3)	69.6 (58.2–79.5)	0.590	0.184

MCV-Mean corpuscular volume, MPV- Mean platelet volume, MCH –Mean corpuscular haemoglobin, PDW – platelet width distribution, RBC –red blood cell, PMR –platelet/monocyte ratio, NLR- neutrophil/lymphocyte ratio, PLR-platelet/lymphocyte ratio, LMR –lymphocyte/monocyte ratio, WNR –white cell/neutrophil ratio, Se-Sensitivity, Sp-Specificity, AUC-area under curve and CI- confidence interval. $^{\Phi}$X 10^3per microlitre, $^{\beta}$X 10^6per microlitre, g/dl – grams per decilitre. *Statistically significant result.

3.1. Characteristics of study participants

The median age of study participants was 34 (interquartile range (IQR): 27–39) years and 52.7% (87/165) were males. Of the study participants, 111 (67.3%) were HIV positive. Cases and controls differed in regards to residence ($p = 0.031$), bacillary load grade ($p < 0.001$) and the MCV ($p = 0.021$). The other characteristics and hemogram parameters of study participants are shown in table 1 and table 2 respectively. There was weak correlation between the MCV with bacillary load (r_s = -0. 264, $p = 0.001$) and residence (r_s = -0.159, $p = 0.044$) as well as between residence with bacillary load ($r_s = 0.162$, $p = 0.045$). At conditional logistic regression analysis, only very low/low bacillary load (adjusted odds ratio = 7.47 95% confidence interval (2.32 – 24.08), $p = 0.001$) was associated with RR – TB (table 3).

3.2. Sensitivity, specificity and AUC of the MCV and CD4/CD8 ratio

At a cut-off of > 74.6 femtolitres (fl), the sensitivity, specificity and AUC of the MCV was 88.9%, 34% and 0.607 ($p = 0.021$) respectively. Among the HIV positive participants, the sensitivity, specificity and AUC of the MCV (cut-off of > 72.5 fl) was 97.2%, 22.2% and 0.608 ($p = 0.061$). Similarly, the sensitivity, specificity and AUC of the CD4/CD8 ratio at a cut-off of > 0.40 was 67.3%, 50.0% and 0.559 ($p = 0.199$) respectively. At the same cut off, the CD4/CD8 ratio had a respective sensitivity, specificity and AUC of 54.1%, 71.6% and 0.628 ($p = 0.024$) among the HIV positive participants. The sensitivity, specificity and AUC of other hemogram parameters are shown in Table 4. The ROC curves for the MCV and CD4/CD8 ratio on the overall and among the HIV positive participants are shown in Fig. 2, Fig. 3, Fig. 4 and Fig. 5 in the appendix.

4. Discussion

In this study we evaluated the sensitivity and specificity of the MCV and CD4/CD8 ratio in discriminating between RR-TB and RS-TB. The MCV demonstrated a high sensitivity (88.9%) for RR-TB that seemed to increase among HIV positive participants (97.2%). However, the specificity was very low. Therefore, the diagnostic value of the MCV is low due to low diagnostic accuracy. If bacteriologically confirmed TB patients with an MCV > 74.6 fl are prioritised for referral for drug susceptibility testing, the low specificity of the MCV implies that TB patients may falsely be classified as having RR – TB. This may increase the rate of unnecessary referral for DST. Moreover, the optimal cut-off, at which we found a high sensitivity, is too low compared to the median MCV among patients with RR – TB and RS – TB. This further demonstrates the low utility of the test. Additionally, lower health facilities would still need infrastructural and technical competence to perform haematological tests for MCV and may therefore not be cost effective as well.

It was apparent from our analyses that the observed significant difference in the median MCV between the cases and controls was confounded by bacillary load and rural residence. Being a marker of pulmonary inflammation, the MCV could be affected by the bacillary load in the lungs; with higher bacillary loads correlating with microcytosis (low MCV) [15]. Our results suggest this negative correlation, although the strength of correlation was weak. From our data, it is unclear why cases had low bacillary load. The low bacillary load observed in our cases is likely due to low biological fitness of drug resistant strains of *Mycobacterium tuberculosis* whereby these strains have slow growth rates [37]. Interestingly, haemoglobin levels and the mean corpuscular haemoglobin were not statistically different between cases and controls. It is therefore likely that the difference in the MCV observed was not due to iron, vitamin B12 or other nutritional deficiencies that cause anaemia. Besides, the MCV poorly predicts with vitamin B12 deficiency related anaemia and iron deficiency among patients with co-existing medical conditions [38–39].

The high sensitivity of the MCV that we observed among HIV positive individuals did not reach statistical significance possibly due to a small sample size. Although HIV related macrocytosis is often observed in the context of zidovudine (AZT) chemotherapy [40]), the proportions of cases and controls who were receiving an AZT containing anti-retroviral therapy did not differ significantly in our study. The sensitivity of the MCV for RR-TB among HIV positive individuals needs further evaluation with a larger sample. Nevertheless, the high proportion of HIV/DR-TB co-infection in our study is consistent with the high burden of HIV among DR-TB patients in Sub-Saharan Africa [41] and supports the generalizability of our findings in HIV/DR-TB high burdened settings. Cases with RR-TB were equally distributed with regards to rural and urban residence contrary to observations that DR-TB is more prevalent in urban areas [42]. This is because the study site is a referral center for DR-TB treatment from rural areas of the country; underscoring the need

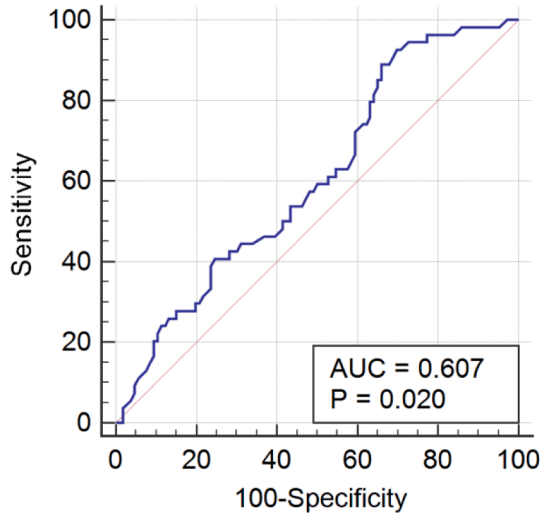

Fig. 2. ROC curve for sensitivity Versus 1-Specificity of MCV as a biomarker in predicting RR-TB on the overall.

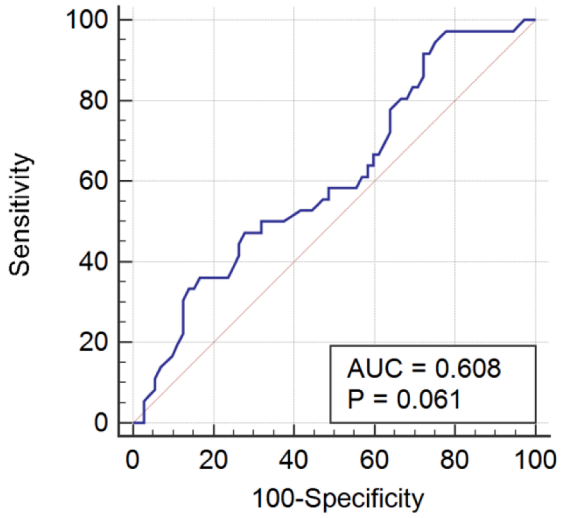

Fig. 3. ROC curve for sensitivity Versus 1-Specificity of MCV as a biomarker in predicting RR-TB among HIV positive individuals.

for simple diagnostic tests in low level facilities to facilitate early referral.

Changes in the CD4/CD8 ratio among HIV positive individuals have been linked to several pulmonary conditions: lung cancer [43], emphysema [44] and COPD [45]. Also, the CD4/CD8 ratio of < 0.7 predicts HIV infection with a sensitivity of 100% and specificity of 94% among tuberculosis patients [46]. It is unknown whether the predictive value of the CD4/CD8 ratio is different between RR-TB and RS-TB patients co-infected with HIV. Our results suggest that the CD4/CD8 ratio is able to discriminate between RR-TB and RS-TB among HIV positive individuals albeit with a low sensitivity. This limits its utility as a screening test.

A key limitation of our study is the small sample size that could have affected our ability to observe statistical significance in the diagnostic performance of other hemogram parameters. Also, the MCV measurement is affected by hyperlipemia, hyperglycaemia, uremia and other biochemical factors which we did not evaluate for [47].

5. Conclusion

The MCV at a cut-off of 74.6 fl had a high sensitivity for RR-TB but very low specificity. Its utility as a screening test for RR-TB among bacteriologically confirmed TB patients is therefore likely to be low. The CD4/CD8 ratio had a low sensitivity and specificity for RR-TB as well. There is still need for simple and cost effective tests that can be used to screen for DR – TB after confirming TB, by say microscopy, in settings where TB DST is unavailable.

Ethical Statement

Study participants provided written informed consent to participate in the primary study that included consent for secondary analyses. The study was approved by the Department of Internal Medicine Scientific Review Committee (SRC) and the School of Medicine Research and Ethics Committee of Makerere University College of Health Sciences.

CRediT authorship contribution statement

Joseph Baruch Baluku: Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Writing - original draft, Writing - review & editing. **Joseph Musaazi:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - review & editing. **Rose Mulwana:** Data curation, Project administration, Writing - review & editing. **Derrick Bengo:** Data curation, Methodology, Writing - review & editing. **Christine Sekaggya Wiltshire:** Methodology, Supervision, Validation, Writing - review & editing. **Irene Andia-Biraro:** Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing - review & editing.

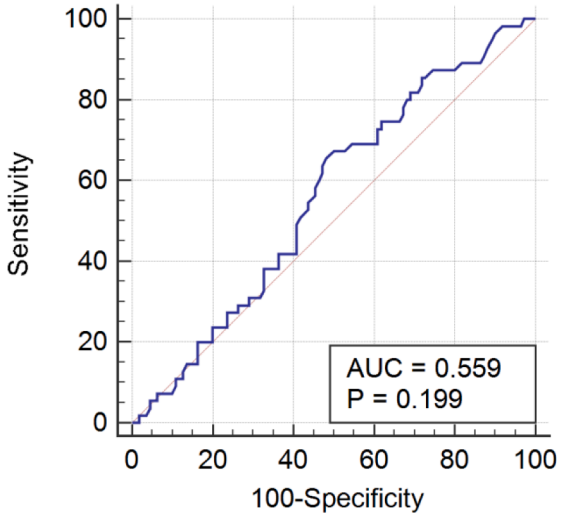

Fig. 4. ROC curve for sensitivity Versus 1-Specificity of CD4/CD8 ratio in predicting RR-TB on the over all.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix:. Receiver operating characteristic curves for the MCV and CD4/CD8 ratio

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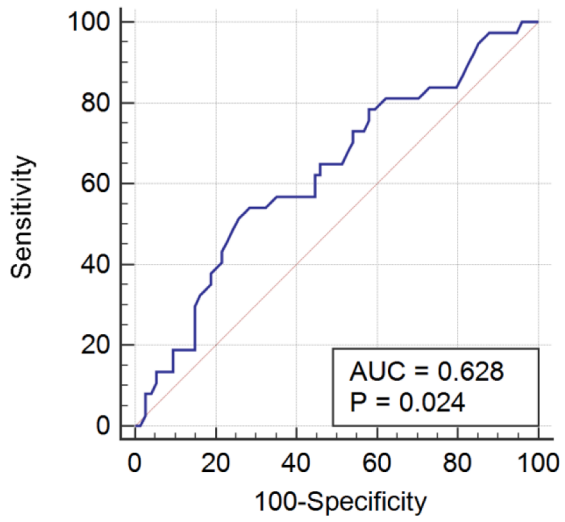

Fig. 5. ROC curve for sensitivity Versus 1-Specificity of CD4/CD8 ratio as a biomarker in predicting RR-TB among HIV positive Participants.

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