Monocyte to lymphocyte ratio and hemoglobin level to predict TB after ART initiation

Sivaporn Gatechompol[1,2,3], Stephen J. Kerr[1,4], Sandra Wagner Cardoso[5], Wadzanai Samaneka[6], Srikanth Tripathy[7], Cecilia Kanyama[8], Mulinda Nyirenda[9], Patcharaphan Sugandhavesa[10], Andre Machado[11], Frank van Leth[12], Thomas Campbell[13] , Susan Swindells[14], Anchalee Avihingsanon[1,2], Frank Cobelens[3], for the ACTG DR067 team

[1]HIV–NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand, [2]Center of Excellence in Tuberculosis, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3] Amsterdam Institute for Global Health and Development, University of Amsterdam, Amsterdam, Netherlands, [4]Biostatistics Excellence Centre, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [5]Evandro Chagas Clinical Research Institute, Fiocruz, Rio de Janeiro, Brazil, [6] University of Zimbabwe College of Health Sciences, Harare, Zimbabwe, [7]National AIDS Research Institute, Pune, India, [8]Kamuzu Central Hospital, Lilongwe, Malawi, [9] College of Medicine- Johns Hopkins Research Project, Blantyre, Malawi, [10]Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand, [11] Hospital Nossa Senhora da Conceicao-GHC, Porto Alegre, Brazil, [12]Vrije Universiteit; Amsterdam Public Health research institute, Amsterdam, Netherland[13]University of Colorado School of Medicine, Aurora, USA,[14]University of Nebraska Medical Center, Omaha, USA.

BACKGROUND

- Tuberculosis (TB) is an important cause of morbidity and mortality in people with HIV (PWH).
- A prediction test that accurately identified those at risk of active TB would allow targeted chemoprophylaxis.
- The monocyte to lymphocyte ratio (MLR) and hemoglobin level collected routinely in HIV care both display an ability to predict active TB development.

METHODS

- We previously identified that an MLR threshold ≥ 0.23 optimally predicted incident TB after ART initiation[1].
- In this study, we used ACTG A5175 trial data as a validation cohort. We assessed the utility of baseline MLR and anemia severity, alone and in combination, for predicting incident TB in PWH in the first year after ART initiation.
- In brief, A5175 was an open-label randomized controlled trial that enrolled participants from the US and the low- and middle-income countries to prospectively evaluate the efficacy of protease inhibitor and non-nucleoside reverse transcriptase based regimens as initial treatment for PWH.
- Participants starting ART were included in this analysis if they had no active TB at study entry or the 12 months before enrollment.
- Cox regression was used to assess associations of MLR and anemia severity with incident TB. Harrell's C index was used to describe single model discrimination and model prediction was compared using log-likelihood tests and and Akaike's Information Criteria (AIC).
- The MLR was defined as the absolute monocyte count divided by the absolute lymphocyte count. Hemoglobin values at baseline visit were used to categorized anemia according to the World Health Organization (WHO) criteria: No anemia (≥13.0 g/dL for men and ≥12.0 g/dL for women), mild anemia (11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women), moderate anemia (8.0–10.9 g/dL for both sexes) and severe anemia (<8.0 g/dL for both sexes).

CONCLUSIONS

- *Addition of MLR to anemia severity improved prediction of incident TB.*
- *Routinely measured MLR and hemoglobin levels should be accessed at ART initiation for identifying patients at high risk of developing TB disease to guide diagnostic and management decisions.*

RESULTS

- Total of 1,455 participants were included. Baseline characteristics are shown in table1.
- Fifty-four participants were diagnosed with TB within 1 year of ART initiation. The hazard ratio (HR) for incident TB was 1.77[95% confidence interval (CI); 1.01-3.07]; p = 0.04 for those with MLR ≥0.23 versus MLR <0.23.
- Compared to non anemic participants, the HR for mild/moderate anemia was 3.35[95%CI; 1.78-6.29; p <0.001] and 18.16[95%CI; 5.17-63.77; p <0.001] for severe anemia. After combining parameters, there were small increases in adjusted HR (aHR) for MLR ≥0.23 to 1.83[95%CI; 1.05-3.18], and increasing degrees of anemia severity (aHR 3.38[95%CI; 1.80-6.35] for mild/moderate anemia and 19.09[95%CI; 5.43-67.12] for severe anemia, respectively).
- C indices (95%CI) were 0.57(0.51–0.63), 0.66(0.60–0.72) and 0.69(0.62-0.76) for MLR, anemia severity and both factors combined, respectively.
- The model AIC decreased from 762.34 for anemia severity alone to 759.56 after addition of MLR (P=0.03).

Table 2: Cox proportional hazard model and C index of MLR and anemia severity for incident TB among participants

Model	Hazard Ratio (95% CI)	P-value	Harrell's C index	95% CI
1.MLR (≥ 0.23 vs < 0.23)	1.77 (1.02-3.07)	0.043	0.57	0.51 - 0.63
2. Anemia severity			0.66	0.60 - 0.72
• Mild-Moderate anemia	3.35 (1.78-6.29)	<0.001		
• Severe anemia	18.16 (5.17-63.77)	<0.001		
3. MLR + Anemia severity			0.69	0.62 - 0.76
• MLR	1.83 (1.05-3.18)	0.032		
• Mild-Moderate anemia	3.38 (1.80-6.35)	<0.001		
• Severe anemia	19.09 (5.43-67.12)	<0.001		

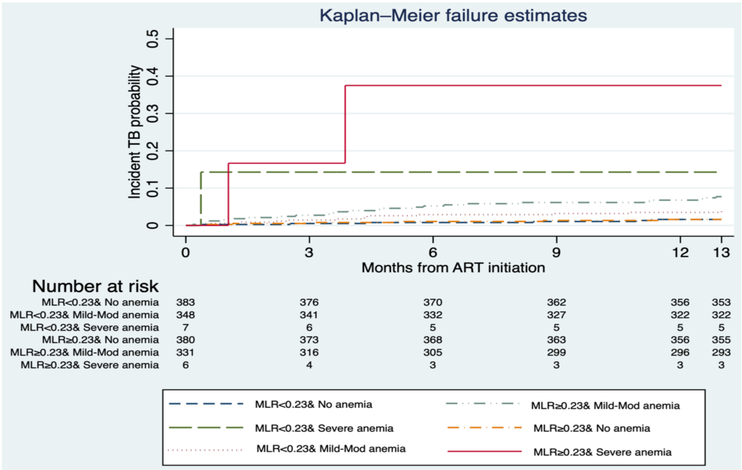
MLR, monocyte to lymphocyte ratio; AIC, Akaike's Information Criteria

Table 1: Characteristics of the participants at ART initiation

Characteristics	Total (N=1,455)	Characteristics	Total (N=1,455)
Age (years), median (IQR)	34.0 (29.0-41.0)	**BMI (kg/m²), median (IQR)**	22.5 (20.3- 25.2)
Females, N (%)	691 (47.5)	**CD4 cell count (cells/mm³), median (IQR)**	174 (92-234)
Country, N (%)		**HIV-RNA (log $_{10}$ copies/ml), median (IQR)**	5.0 (4.5-5.4)
Peru	129 (8.9)	**HBsAg positive, N (%)**	80 (5.5)
Malawi	208 (14.3)	**Baseline TB status, N (%)**	
India	197 (13.5)	• No history of TB	1,286 (88.4)
Thailand	99 (6.8)	• History of TB episode >12 months prior to ART initiation	169 (11.6)
South Africa	185 (12.7)	**Treatment arm, N (%)**	
Brazil	227 (15.6)	• EFV+3TC/AZT	477 (32.8)
Haiti	93 (6.4)	• ATV+DDI+FTC	491 (33.8)
Zimbabwe	108 (7.4)	• EFV+FTC/TDF	487 (33.5)
United States	209 (14.4)		
Baseline Hb (g/dL), median(IQR)	12.5 (11.2-13.8)		
CD4 cell count (cells/mm³), median (IQR)	174 (92-234)		

BMI, body mass index; EFV, Efavirenz; 3TC/AZT, lamivudine/zidovudine; ATV, Atazanavir; DDI, didanosine; FTC, emtricitabine; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate

Fig.1 Kaplan-Meier curve showing the probability of incident TB after ART initiation by baseline MLR and anemia severity category



REFERENCE

1. Gatechompol S, Sophonphan J, Kerr SJ, Ubolyam S, Avihingsanon A, van Leth F, et al. Monocyte-to-lymphocyte ratio as a predictor of TB among people living with HIV. Int J Tuberc Lung Dis. 2021;25(11):933-8.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all participants and the members of ACTG A5175 team. This work was funded by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Numbers UM1 AI068634, UM1 AI068636 and UM1 AI106701 and CRS 31802 - Thai Red Cross AIDS Research Centre (TRC-ARC) CRS, (CTU grant number 5UM1AI069399).