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Monocyte-to-lymphocyte ratio as a predictor of TB among people living with HIV

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SUMMARY

BACKGROUND: Diagnostic tools to identify incipient or subclinical TB stages will be helpful for preventive intervention. A simple biomarker to predict TB may be the monocytes to lymphocytes ratio (ML ratio) in peripheral blood.

METHODS: We assessed the relationship between multiple time-updated ML ratio measurements and incidence of TB in people living with HIV (PLWH) after antiretroviral therapy (ART) was initiated. The ML ratio was updated at least every 6 months. TB incidence with corresponding 95% confidence intervals stratified according to time-updated ML ratio was calculated using ML ratio in quartiles.

RESULTS: A total of 1305 PLWH were included in the analyses: 46 had incident TB and 1259 remained TB-free. The TB incidence rate was 10.3 (95% CI 7.1–14.9) cases/1000 patient-years (PYR) among participants with ML ratio ≥0.25 compared with 1.1/1000 PYR (95% CI 0.4–2.9) among those with ML ratio <0.15. At cut-point 0.23, the ML ratio provided a diagnostic area under the receiver operating characteristics curve (AROC) of 0.849 (95% CI 0.784–0.914) and a sensitivity of 85% and specificity of 71%.

CONCLUSION: Increased ML ratio was predictive of incident TB among PLWH on or after ART. The ML ratio can be a simple tool to stratify the risk of TB in PLWH.

KEY WORDS: ML ratio; tuberculosis; HIV; monocytes; predictor

In 2019, an estimated 1.4 million people died from TB worldwide, including 208,000 people living with HIV (PLWH).[1] In Thailand, there were 10,000 incident TB cases and 1,900 deaths among PLWH in 2019. Approximately one third of the global population are thought to have latent TB infection (LTBI).[2] Many studies suggest that PLWH with subclinical TB can rapidly progress to active TB disease within weeks to months after starting combination antiretroviral therapy (ART).[3–5] A prospective cohort study has demonstrated that host blood transcriptomic signature can be used to predict the risk of incident tuberculosis within 15 months among PLWH.[6] It has recently been proposed that considering the additional spectrum of TB infection from initial infection until the development of active disease is necessary to clearly understand the pathophysiology of TB infection.[7,8]

Incipient TB infection is an infection with *Mycobacterium tuberculosis*; metabolic activity indicates ongoing progression of infection but absence of radiographic abnormalities, microbiologic evidence or clinical symptoms consistent with active TB disease. Subclinical TB disease is a state of TB disease in which radiographic abnormalities and microbiologic evidence can be detected but clinical symptoms consistent with active TB disease are absent.[8] Identification of these asymptomatic stages might impact the development of diagnostic TB biomarkers and could be the targets for preventive intervention.[9] However, diagnostic tools for either incipient or subclinical TB are still under investigation.[10–12]

A number of sources of evidence suggest that a simple biomarker to predict active TB may be the ratio of monocytes to lymphocytes (ML ratio). In a mycobacterial growth inhibition assay, transcriptome analysis of monocytes suggests that the ML ratio is a marker of monocyte function, and elevated ratios are associated with an enrichment of interferon-associated transcripts in monocytes.[13] A previous cohort study found that HIV-negative household contacts with pulmonary TB had high levels of peripheral monocytes before developing active TB.[14] In addition, an elevated ML ratio was associated with an

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increased risk of TB disease: a high ML ratio could predict the development of active TB among South African children.[15] Moreover, the ML ratio before starting ART could predict the risk of developing active TB in a prospective cohort of PLWH in South Africa.[16]

Despite evidence that the ML ratio is an easy-to-apply predictor, only a limited number of studies have evaluated the ML ratio in HIV-infected populations.[16,17] We evaluated whether the ML ratio collected routinely during general HIV care visits in our long-term HIV cohort, could predict the occurrence of active TB disease in PLWH on ART over a period of ≥6 months.

METHODS

Study design and participants

This is a post-hoc analysis of data from the HIV-NAT 006 cohort. HIV-NAT 006 is a prospective, clinic-based cohort that has enrolled HIV-infected adults aged >18 years since 1996 (Clinicaltrials.gov NCT00411983). In this cohort, participants were seen every 6 months at HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand. Care for HIV infection was provided according to Thai national treatment guidelines current at each time during follow-up.[18–20] At each cohort visit, the following clinical parameters were routinely collected: body temperature, body weight, body mass index (BMI) and physical examination. Participants underwent blood testing for full differential blood counts, lipid profile, creatinine and alanine aminotransferase (ALT) every 6 months, and CD4, CD8 and HIV RNA every 12 months. Participants were selected for this analysis if they had an ML ratio available at the time when they started ART and had at least one follow-up visit. Participants with active TB at the time of ART initiation were excluded.

Ethical approval

This cohort was approved by the medical ethics committee of Chulalongkorn University, Bangkok, Thailand. This study was conducted according to the Declaration of Helsinki and Good Clinical Practice. All participants provided written informed consent before any procedures were conducted.

TB definition and diagnosis

All cohort participants were screened for TB before starting ART. During the follow-up period, participants with symptoms and/or signs of pulmonary or extrapulmonary TB were assessed according to Thailand's national TB treatment guidelines,[21,22] which included physical examination, chest radiography, sputum smear microscopy, culture for *M. tuberculosis* and/or Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) as indicated. The diagnosis of TB for this analysis was made using the following criteria: 1) bacteriologically confirmed using smear microscopy, culture or Xpert, and 2) clinically diagnosed without bacteriological confirmation by the clinician, received TB treatment after which there was a clinical response. TB preventive therapy was not routinely provided in accordance with local guidelines.

Full differential blood counts

Full blood counts were performed by a clinical diagnostic laboratory that has been accredited by the College of American Pathologists (CAP) using a 5-part differential haematology analyser (Sysmex Model XN; Sysmex Corporation, Kobe, Japan). The laboratory's internal quality control was performed twice daily at three levels (low, normal and high), and external quality control was done three times a year through CAP.

Statistical analysis

We used the ML ratio as the primary exposure. It was defined as the absolute monocyte count divided by the absolute lymphocyte count. We used time to event analysis to assess the association between ML ratio and incident TB, in which the ML ratio was considered a time-varying exposure and updated at each of the 6-month clinic visits. ML ratios were categorised according to quartiles from all observations (<0.15, 0.15–0.19, 0.20–0.24, ≥0.25) to understand transition between categories; time-at-risk started at the time of ART initiation. Patients who died or were lost to follow up were censored at their last clinic visit. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with their 95% confidence intervals (95% CIs) for factors associated with incident TB. In addition to the primary exposure (ML ratio), we assessed associations between incident TB and BMI (time-varying, dichotomised at 18.5 kg/m^2), CD4 count (time-varying, dichotomised at 100 cells/mm^3) and plasma viral load (time-varying, dichotomised at 50 copies/mL). of BMI and CD4 cell count were dichotomised, as these levels are known to be associated with incident TB. Plasma viral load was dichotomised to reflect that the majority of participants in the cohort had virological suppression. Fixed covariates included age, sex and Centers for Disease Control and Prevention (CDC) classification for HIV Infection[23] at ART initiation. If TB was diagnosed outside of the scheduled 6-month visit, the ML ratio from the previous visit was used. Covariates with $P < 0.1$ in univariable models were included in a multivariable model to assess their association with incident TB. We formally tested the proportional hazards assumption overall, and separately for each variable in the final model, by assessing whether the log hazard-ratio function

Table 1 Characteristics of the participants at ART initiation

	Total (n = 1305) n (%)
Age, years, median [IQR]	35.8 [30.8–41.5]
Male sex,	801 (61.4)
BMI, kg/m^2, median [IQR]	21.6 [19.8–23.7]
Ever smoked	406 (31.1)
Ever consumed alcohol	385 (35.6)
History of substance use	29 (2.2)
HBV co-infection	180 (13.8)
HCV co-infection	104 (8)
CD4 cell count, cells/mm^3, median [IQR]	274 [169–406]
HIV-RNA, $\log_{10}$ copies/mL, median [IQR]	4.6 [4.1–5.1]
CDC class C	72 (5.5)
Baseline ART containing regimens	
NRTI	1241 (95)
NNRTI	576 (44)
Protease inhibitor	322 (25)
Integrase inhibitor	88 (7)

ART = antiretroviral therapy; IQR = interquartile range; BMI = body mass index; HBV = hepatitis B virus; HCV = hepatitis C virus; CDC = Centers for Disease Control and Prevention; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-NRTI.

was constant over time.[24] We conducted two sensitivity analyses. First, we assessed the robustness of the findings if the analysis was limited to TB patients with bacteriologically confirmed TB. Second, we used a time-dependent receiver operating characteristics (ROC) curve to assess the optimal cut-off of the ML ratio for TB diagnosis based on Youden's index using Heagerty, Lumley and Pepe's methodology.[25] Sensitivity, specificity and the discriminative ability of the model assessed by the area under the ROC curve (AROC) were calculated at the median and 99th percentile of follow-up time (5 years and 18 years, respectively) for comparison; the 95% CIs around these estimates were obtained by bootstrapping the estimates with 20 replications. Analysis was conducted using Stata v15.1 (Stata Corp, College Station, TX, USA).

RESULTS

Participant characteristics

From January 2000 to August 2019, 2,021 PLWH initiated ART at the HIV-NAT clinic: 155 were diagnosed with TB prior to ART initiation and 561 were excluded for lack of ML ratio measurements at baseline. Thus, 1,305 PLWH were included in the analyses (Table 1). The median age was 35.8 years (interquartile range [IQR] 30.8–41.5); 801 (61%) were male. The median baseline CD4 cell count was 274 cells/mm^3 (IQR 169–406), and the median duration of follow-up was 9.3 years (IQR 5.4–15.3). Over a total of 13,261 person-years of follow-up, 46 participants were diagnosed with TB, for a crude TB incidence of 3.5 per 1,000 patient-years (PYR) (95% CI 2.6–4.6) of follow-up. Of these, respectively 30% and 70% of TB cases were bacteriologically confirmed and clinically diagnosed. The median time interval between last ML ratio measurement and time of TB diagnosis was 1.8 months (IQR 1.5–3.4).

Table 2 TB incidence rates after ART initiation stratified by time updated ML ratio

ML ratio	Total number of TB incidence	PY at risk	Rate per 1,000 PYs (95% CI)
<0.15	4	3,632.1	1.1 (0.4–2.9)
0.15–0.19	3	4,149.5	0.7 (0.2–2.2)
0.20–0.24	11	2,756.7	4.0 (2.2–7.2)
≥0.25	28	2,722.7	10.3 (7.1–14.9)
Total	46	13,261	3.5 (2.6–4.6)

ART = antiretroviral therapy; ML = monocytes to lymphocytes; PY = patient-year; CI = confidence interval.

TB incidence rate and time-updated ML ratio

The TB incidence rate after ART initiation was 10.3/1000 PYR (95% CI 7.1–14.9) among participants with ML ratio ≥0.25, and 4.0/1000 PYR (95% CI 2.2–7.2) among those with an ML ratio of 0.20–0.24, compared with 1.1/1000 PYR (95% CI 0.4–2.9) and 0.7/1000 PYR (95% CI 0.2–2.2) among participants with an ML ratio <0.15 and 0.15–0.19, respectively (Table 2, Figures 1 and 2).

Twenty-seven of 46 TB diagnoses (59%) were within 6 months after starting ART. In this group, 14/27 (52%) had ML ratio ≥0.25 and 7/27 (26%) had ML ratio of 0.2–0.24 at baseline. The median time interval from baseline to time of TB diagnosis in this group was 18 days (IQR 14–29), consistent with unmasking TB immune reconstitution inflammatory syndrome.[26] Among those who developed TB >6 months after ART initiation, the median time from ART initiation to TB diagnosis was 6.2 years (IQR 3.1–10.5). The median interval between date of ML ratio testing and TB diagnosis was 106 days (IQR 71–164).

Sensitivity analyses

In an analysis excluding patients unless their TB was bacteriologically confirmed, the results were consistent with the primary analysis. Using time-dependent ROC analyses, the optimal MLR cut-point was 0.23 at median follow-up of 5 years, with a sensitivity of 68%, specificity of 74% and AROC of 0.743 (95% CI 0.68–0.81). After 18 years of follow-up, the optimal cut-point was also 0.23, with a sensitivity of 85%, specificity of 71% and AROC of 0.849 (95% CI 0.784–0.914).

Predictors for incident TB after ART initiation

In a univariable model, compared to patients with a ML ratio <0.15, the unadjusted HR for incident TB was 4.33 (95% CI 1.37–13.61) in those with an ML ratio of 0.20–0.24, and 11.1 (95% CI 3.88–31.78) in

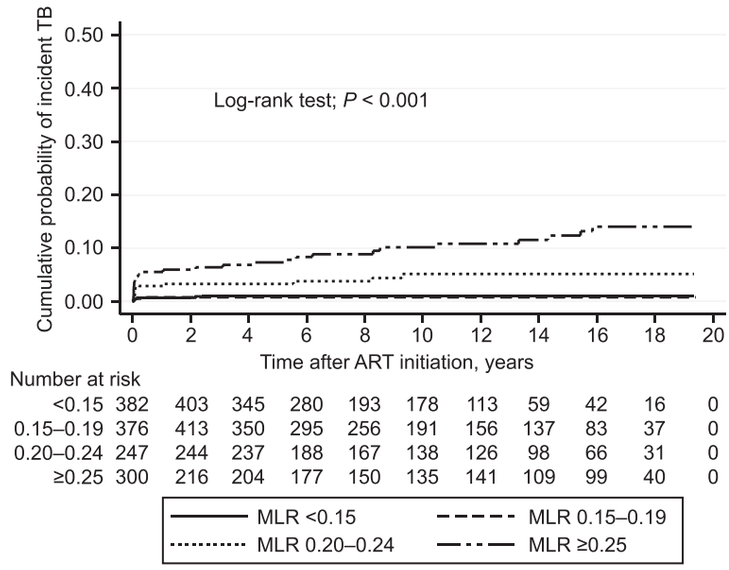

Figure 1 Kaplan–Meier curve showing the cumulative probability of incident TB after ART initiation by time-updated ML ratio category. ART = antiretroviral therapy; ML = monocytes-to-lymphocytes.

those with ML ratio ≥0.25. Adjusting these estimates for CDC class at start of ART and most recent CD4 cell count and plasma viral load changed the HR to respectively 3.87 (95% CI 1.23–12.23; $P = 0.02$) and 9.07 (95%CI 3.12–26.34; $P < 0.001$) among patients with ML ratios of 0.20–0.24 and ≥0.25, compared to the reference group with ML ratio <0.15. In addition, baseline CDC class C (adjusted hazard ratio [aHR] 3.73, 95% CI 1.87–7.44; $P < 0.001$) and most recent HIV viral load ≥50 copies/ml (aHR 4.44, 95% CI 1.66–11.84; $P = 0.003$) were also independent predictors of incident TB (Table 3). We found no significant association between incident TB and age at ART initiation, sex- or time-updated BMI.

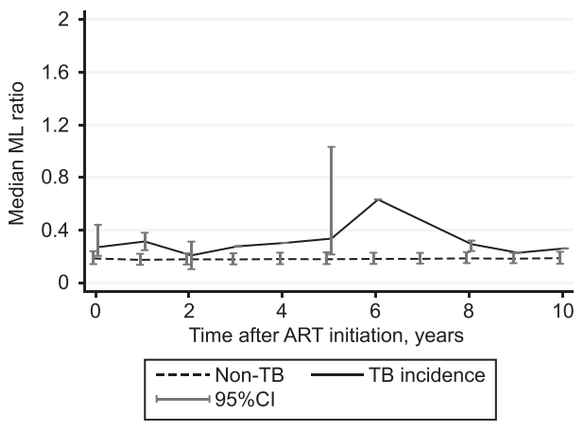

Figure 2 Median ML ratio in cohort participants who developed TB and cohort participants who did not develop TB. ML = monocytes-to-lymphocytes; ART = antiretroviral therapy; CI = confidence interval.

DISCUSSION

Clinical presentation of TB disease can be heterogeneous depending on the host's immune status. HIV infection is the strongest individual-level risk factor and a major driver of the TB epidemic.[27] A test to predict development of TB in PLWH could facilitate the early diagnosis and treatment of clinical TB. The WHO has defined the performance characteristics for a target product profile of a test to predict progression from TB infection to active TB disease.[28] In our long-term HIV cohort, we found that ML ratio routinely collected during general HIV care was a predictor of the occurrence of TB disease. When the ML ratio is categorised in quartiles, the highest risk was associated with ML ratio >0.25, a ratio consistent with the optimum ML ratio of 0.23 derived from a time-dependent ROC curve over 18 years of follow-up, with an AROC of 0.849. Participants on ART with a recent (within at least past 6 months) ML ratio of ≥0.25 were at the highest risk for incident TB after adjusting for CD4 count, detectable viral load and clinical stage at ART initiation. Furthermore, the ML ratio at ART initiation was higher in those who developed TB than in those who did not. As the majority of TB cases in our study were diagnosed in the first 6 months of ART, this likely reflects unmasking TB disease after ART initiation. Nevertheless, ML ratio was high in these patients when ART was initiated, despite the absence of clinical symptoms or diagnostic test results that suggested TB infection.

In a meta-analysis, the sensitivity for predicting active TB was 72% (95% CI 58–83) for both ELISpot and the tuberculin skin test (TST), while specificity

Table 3 Cox proportional hazard model for associated factors with incident TB among participants

	Univariable		Multivariable	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
At ART initiation				
Age, years	0.99 (0.95–1.03)	0.70		
Male sex	1.08 (0.60–1.96)	0.78		
CDC class C	6.22 (3.28–12.01)	<0.001	3.73 (1.87–7.44)	<0.001
Time updated variables				
BMI <18.5 kg/m^2	2.0 (0.43–9.12)	0.37		
ML ratio group				
<0.15	Reference		Reference	
0.15–0.19	0.75 (0.17–3.36)	0.71	0.73 (0.16–3.26)	0.68
0.20–0.24	4.33 (1.37–13.61)	0.01	3.87 (1.23–12.23)	0.02
≥0.25	11.1 (3.88–31.78)	<0.001	9.07 (3.12–26.34)	<0.001
CD4 cell count <100 cell/mm^3	5.78 (2.32–14.39)	<0.001	1.83 (0.65–5.18)	0.25
HIV–RNA ≥50 copies/mL	6.71 (2.66–16.98)	<0.001	4.44 (1.66–11.84)	0.003

HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; BMI = body mass index; ML = monocytes to lymphocytes.

was only 50% (95% CI 41–58) for ELISpot and 41% (95% CI 30–54) for TST.[29] In our study, at a cut-off of 0.23, the ML ratio had similar sensitivity of 80% but a higher specificity of 76%. Using ML ratio as an adjunct to other screening tools may help to stratify TB risk more accurately, especially in people who have difficulty providing sputum or other specimens. High ML ratios should alert physicians that the patients are at risk of developing TB, so that these patients can be intensively monitored and TB treatment initiated early if indicated.

Monocytes proliferate in response to mycobacterial growth before migrating and differentiating into macrophages.[30] In recent studies, a higher ML ratio was associated with mycobacterial growth in vitro, and an elevated ratio of gene expression transcripts of monocytes was associated with TB disease in vivo.[13] In this latter study, the expression of gene signatures consistent with TB-related inflammation was up-regulated in monocytes isolated from TB progressors prior to disease manifestation.[31] Together, these findings suggest that an increased ML ratio reflects an inflammatory response to *M. tuberculosis* and thereby incipient TB disease, rather than increased susceptibility to TB disease progression that is yet to occur.[32]

A strength of our study was that it was conducted in large cohort of PLWH in a high TB burden country, and patients were regularly followed up in a research environment. Nevertheless, there were some limitations to our study. First, we had a low incidence of TB in our cohort, which affected the precision of our estimates, resulting in wide CIs around the HRs. Second, there was a low frequency (30%) of bacteriologically confirmed TB cases, the remainder were treated based on clinical diagnostic criteria. It is possible some of these patients had pathogens other than *M. tuberculosis* or may have had non-infectious clinical conditions. Finally, approximately 30% of the total study cohort did not have ML ratios available at ART initiation, mostly because their study protocols did not require the test, so these patients were excluded from the analysis.

Our study demonstrated that the ML ratio in routine clinical care may be a useful tool to stratify TB risk in PLWH. However, diagnostic threshold values of ML ratio need further investigation. A study among HIV-infected children found that ML ratio >0.378 identified children with confirmed TB with 77% sensitivity and 78% specificity.[33] Furthermore, a study of non-HIV-infected adults found that ML ratio at a cut-off value of 0.285 had high sensitivity and specificity (respectively 91% and 94%) to identify patients with culture-confirmed TB.[34] These findings are consistent with our findings, suggesting that the ML ratio threshold for predicting TB disease is more than 0.25. Validation studies should be conducted in prospective patient cohorts to evaluate these cut-offs for prediction or early diagnosis of TB disease in PLWH, potentially stratified by HIV parameters such as CD4 count.

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Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : Les outils diagnostiques permettant d'identifier les stades débutants ou infracliniques de la TB seront utiles à la prévention. Le ratio monocytes/lymphocytes (ratio ML) dans le sang périphérique peut servir de marqueur biologique de prédiction de la TB.

MÉTHODES : Nous avons évalué la relation entre des mesures du ratio ML répétées au fil du temps et l'incidence de la TB chez les personnes vivant avec le VIH (PLWH) après instauration du traitement antirétroviral (ART). Le ratio ML a été mis à jour au moins tous les 6 mois. L'incidence de la TB (et les intervalles de confiance à 95% correspondants) stratifiée en fonction du ratio ML mis à jour au fil du temps a été calculée à l'aide du ratio ML défini par quartiles.

RÉSULTATS : Au total, 1 305 PLWH ont été incluses dans les analyses : 46 étaient atteintes de TB incidente et 1 259 n'étaient pas atteintes de TB. Le taux d'incidence de la TB était de 10,3 (IC 95% 7,1–14,9) cas/1 000 patients-années (PYR) parmi les participants avec ratio ML $\geq$0,25 comparé à 1,1/1 000 PYR (IC 95% 0,4–2,9) parmi ceux ayant un ratio ML <0,15. Au seuil de 0,23, le ratio ML était associé à une aire sous la courbe ROC diagnostique (AROC) de 0,849 (IC 95% 0,784–0,914), à une sensibilité de 85% et à une spécificité de 71%.

CONCLUSION : L'augmentation du ratio ML était une variable explicative de TB incidente chez les PLWH sous ART ou après ART. Le ratio ML peut être un outil facile à utiliser pour stratifier le risque de TB chez les PLWH.

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