RESEARCH ARTICLE

Higher Neutrophil-lymphocyte Ratio in TB/HIV Co-infection Compared to Pulmonary Tuberculosis

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Abstract

BACKGROUND: Neutrophils and lymphocytes play a significant role in inflammation and a high ratio of neutrophils over lymphocytes (NLR) has been used as an inflammatory marker to predict the severity of various diseases. Here we compared the NLR among pulmonary tuberculosis and TB/HIV co-infection.

METHODS: A retrospective cross-sectional study was conducted, included patients with pulmonary TB without cavitation TB (n=50), with cavitation TB (n=50) and HIV co-infection (n=27). Complete blood count was examined, including neutrophils and lymphocyte. NLR was calculated and compared between groups.

RESULTS: Neutrophils were significantly higher (p=0.004) in TB with cavitation compared to those with no cavitation (8.27±1.45 x10^3/µL *vs.* 6.61±1.4 x10^3/µL, respectively); whereas the lymphocytes were similar in both groups, resulting in a significantly higher NLR (p=0.009) in pulmonary TB with cavitation compared to pulmonary TB with no cavitation (5.98±1.85 *vs.* 4.42±1.86, respectively). On the contrary, both neutrophils as well as lymphocyte were significantly lower in TB/HIV compared to pulmonary TB, which for neutrophil were 5.14±2.19 x10^3/µL *vs.* 7.4±1.45 x10^3/µL, respectively (p=0.003) and for lymphocyte (1.02 ±0.57 x10^3/µL *vs.* 1.57±0.64 x10^3/µL, respectively (p=0.001), resulting in a significantly higher (p=0.041) NLR value in TB/HIV (6.05±2.67) compared to pulmonary TB (5.16±1.88).

CONCLUSION: High NLR in pulmonary TB with cavitation as well as in TB with HIV co-infection may be of great interest for biomarker in TB severity. Further study confirming NLR as potential marker is imperative.

KEYWORDS: lymphocyte, neutrophil, NLR, tuberculosis, TB/HIV

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Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) that poses as a public health problem with approximately 10 new million cases annually worldwide.(1) Indonesia ranks second as the country with the highest TB burden where 8.5% of global TB patients reside, after India with 26%.(1) MTb infection in respiratory tract causes innate and adaptive response orchestrating to generate granuloma.(2,3) Granuloma acts as an immunological microenvironment for cellular interaction that prevent bacterial dissemination. (4-6)

Innate immune response plays a central role in the pathology of infectious and inflammatory diseases.(7) Neutrophils have a significant role in the innate immune response to Mtb infection.(8) However, neutrophils are also implicated in immunopathology during Mtb infection.(9) Previous study also explained that neutrophilia among TB patient increased risk of cavity formation.(7) Cavitation is a dangerous consequence of pulmonary TB, associated with high rates of bacterial replication due to high oxygen concentration within the cavity.(10) Cavitation TB also increase the risk to relapse after treatment.(10)

Despite the cavitation that may increase the risk of TB recurrence, human immunodeficiency virus (HIV) co-infection is one of the most important risk factors associated with TB recurrence due to loss or dysfunction of immunity and several other poorly understood mechanisms for immunopathogenesis.(11-13) TB and HIV has bidirectional impact; TB infection among HIV patient cause slowing CD4 recovery and increasing progression to AIDS; in the other hand HIV infection among TB patient also increase TB disease progression.(14) It is estimated that 1.2 million people has died from TB globally, and among these, 17% is HIV infected. In Indonesia, there are 845 thousand new TB cases yearly, and 2.2% of the patients are HIV positive.(1)

In associated with neutrophils, patient with immunocompromised state due to Mtb infection cause the effectiveness of neutrophils encumbered.(8) Furthermore, previous study has shown that as a consequence of diminished numbers of $CD4^+$ T lymphocyte cells, patient with TB/HIV co-infection has decreased level of IFN-γ rather than increased neutrophil.(8,15)

The ratio of neutrophils over lymphocytes (NLR) has been used as an emerging and inflammatory marker in malignancies, infection, and coronary artery disease to predict the severity and mortality.(16-18) In infectious disease, NLR is a better predictor of bacteremia than C-reactive protein (CRP) level, white blood cell and neutrophil count.(17) Furthermore, prognosis of several infectious diseases such as community acquired pneumonia and bacteremia has been correlated with NLR.(19) Clearly, NLR is a readily available biomarker used in clinical practice that has been correlated with severity, mortality and reccurency among several clinical conditions.(20)

Therefore, the aim of this study was to compare the ratio of neutrophils over the lymphocytes among pulmonary TB patient and HIV co-infection.

Methods

Study Design

The design of this study was a retrospective cross-sectional design, using secondary laboratory data collected from patients with pulmonary TB with or without HIV co-infection. This study was approved by Research Ethics Committee, Universitas Padjadjaran with ethical number 653/UN6.KEP/EC/2020.

Sample Size and Inclusion

Data patients with pulmonary TB and TB/HIV were collected in 2016, as part of TANDEM study (*http://www.tandem-fp7.eu/*), were taken using a purposive sampling technique. Pulmonary TB with cavity (n=50) and without cavity (n=50) were selected and matched with gender and age +/- 10 years. In addition, all pulmonary TB patients with HIV co-infection (n=27) were taken. The inclusion criteria were available complete blood data including neutrophil and lymphocyte; whereas incomplete data were excluded.

In brief describing about the TANDEM study, new pulmonary TB patients who were treated at the 45 community health centers with high rates of TB cases in Bandung, West Java, Indonesia were included. After first visit to the clinic and after consent, a careful anamnesis was conducted to collect data on clinical symptoms such as gender, age, smoking status and body mass index. Those who were highly suspected of active TB were further examined for chest radiography, complete blood count and sputum smear, followed by sputum culture. Active pulmonary TB was confirmed with at least one of the following criteria: positive acid-fast bacillus (AFB) smear derived from sputum or positive growth of Mtb in sputum culture. The TB patient was further categorized as newly pulmonary TB patient with or without cavity based on chest radiography result. Additionally, HIV test was conducted upon informed consent for every patient with TB. The TB patients were further categorized as newly pulmonary TB patients with or without HIV co-infection.

Complete Blood Count

Blood samples used in this study was drawn in EDTA tube, then sent to central laboratory of hospital within 2 hours from blood collection. Automatic hematology analyzer (XN-1000 Sysmex Hematology analyzer, Sysmex, Kobe, Japan) was used to measure complete blood count (CBC), including red blood cell (RBC), white blood cell (WBC),

Table 1. Clinical symptoms and radiographic findings among new pulmonary tuberculosis patients at outpatient clinic in Bandung, Indonesia.

Characteristic	TB				TB/HIV (n=27)		*p*-value
	No cavitation (n=50)		With cavitation (n=50)				
	n	%	n	%	n	%	
Gender							
Male	25	(50)	29	(58)	18	(66.6)	0.360
Female	25	(50)	21	(42)	9	(33.4)	
Age							
18-29	19	(38)	19	(38)	13	(48.2)	0.195
30-50	21	(42)	23	(46)	14	(51.8)	
>50	10	(20)	8	(16)	-	-	
Loss of Weight[#]							
≤5 kg	36	(72)	31	(62)	11	(40.7)	0.027*
>5 kg	14	(28)	19	(38)	16	(59.2)	
BMI Category (kg/m^2)							
<18.5	24	(48)	30	(60)	22	(81.4)	0.010*
≥18.5	26	(52)	20	(40)	5	(18.6)	
Clinical Symptoms							
Cough Duration							
≤2 weeks	4	(8)	2	(4)	10	(37.1)	0.000*
≥3 weeks[#]	46	(92)	48	(96)	17	(62.9)	
Haemoptysis							
No	30	(60)	29	(58)	22	(81.5)	0.020*
Mild Haemoptysis	10	(20)	4	(8)	4	(14.8)	
Massive Haemoptysis	10	(20)	17	(34)	1	(3.7)	
Dyspnea							
Yes	29	(58)	34	(68)	18	(66.6)	0.550
No	21	(42)	16	(32)	9	(33.4)	
Night Sweat[#]							
Yes	41	(82)	45	(90)	15	-55.6	0.001*
No	9	(18)	5	(10)	12	-44.4	
Chest X-ray Reading							
Consolidation							
Any	23	(46)	19	(38)	4	(14.8)	0.024*
None	27	(54)	31	(62)	23	(85.2)	
Pleural Effusion							
Yes	5	(10)	5	(10)	11	40.7	0.99
No	45	(90)	45	(90)	16	(59.3)	
Percentage of Visible Lung Affected							
<30%	15	(30)	14	(28)	10	(37.1)	0.067[a]
30-60%	21	(42)	20	(40)	13	(48.1)	
≥60%	14	(28)	16	(32)	4	(14.8)	

[#]Clinical symptom that occurred in more than 75% of cases; **p*-value statistically significant ($p<0.05$); [a]*p*-value calculated using Kruskal-Wallis test.

hemoglobin, and platelet counts, as well as hematocrit levels. A white blood cell was differentiated by flow cytometry method (using a semiconductor laser). A white blood cell was differentiated to lymphocytes, monocytes, eosinophils, basophils, and neutrophils using three channel which were WNR channel, WDF channel, and WPC channel. The proportion percentages of neutrophil and lymphocytes was extracted from this analyzer.

Statistical Analysis

The characteristic and clinical symptoms TB patients with or without cavitation and TB with HIV co-infection were presented as frequencies and percentages and compared among groups using Chi-square and Kruskal-Wallis test. The neutrophils, lymphocytes, NLR among TB patient with and without HIV co-infection were presented in mean and geometric mean with standard deviation, and compared using Mann-Whitney, t-independent test, and Kruskal-Wallis test. Neutrophil, lymphocyte and NLR were also compared among groups in association with the clinical symptom and X-ray findings. The data was analyzed using SPSS program version 22 (IBM Corporation, Armonk, NY, USA) and figures were presented using Prism 9 (GraphPad, GraphPad Software Inc, San Diego, CA, USA)

Results

In total, 127 new pulmonary TB patients were included, consisting of pulmonary TB patients with no cavitation (n=50), with cavitation (n=50) and TB patients with HIV co-infection (n=27). The characteristics, clinical symptoms and X-ray findings of those patients were presented in Table 1. Body mass index (BMI) <18.5 kg/m^2 (p=0.01) and loss of weight >5 kg (p=0.027) were significantly more prevalent in TB/HIV compared to pulmonary TB. Cough duration more than 3 weeks (p<0.001), haemoptysis (p=0.02) and night sweat (p=0.001) were significantly increased in pulmonary TB with cavitation; whereas consolidation was more common in pulmonary TB with no cavitation (p=0.024). However, age, gender, pleural effusion and percentage of visible lung affected were not significantly correlated with any groups (Table 1).

In pulmonary TB, neutrophils (mean 7.4±1.45 x10^3/µL) was significantly higher compared to TB/HIV (mean 5.14±2.19 x10^3/µL) (p=0.003) as shown in Table 2. Moreover, neutrophils in pulmonary TB with cavitation (mean 8.27±1.45 x10^3/µL) was significantly higher (p=0.004) compared to pulmonary TB with no cavitation (mean 6.61±1.40 x10^3/µL) (Figure 1).

Lymphocytes among TB/HIV co-infection were as expected low (mean 1.02±0.57 x10^3/µL). Compared to pulmonary TB (mean 1.57±0.64 x10^3/µL), lymphocytes among TB/HIV co-infection was statistically significantly lower (p=0.001) (Figure 2). Lymphocytes value between pulmonary TB with cavitation and with no cavitation showed no statistical difference (p=0.344) (Table 2).

The NLR was significantly higher (p=0.009) in TB with cavitation (mean 5.98±1.85) compared to TB with no cavitation (mean 4.42±1.86) (Figure 3). Moreover, in TB/HIV, NLR (6.05±2.67) was also significantly higher compared to all pulmonary TB patient (5.16±1.88) with p=0.041 (Figure 3). However, there was no statistically significant difference in NLR between TB/HIV with cavitation TB (p=0.8).

This study also compared neutrophils, lymphocytes and NLR value among all TB patient in association with clinical symptoms, and X-ray findings (Table 3). Neutrophil was significantly higher among TB patient with dyspnea, night sweat, visible lung affected >60%, and cavitation. Moreover, we also found that NLR was significantly higher among TB patient with night sweat and cavitation. However, lymphocyte was not significantly correlated with clinical symptoms and X-ray findings (Table 3).

Table 2. Comparison of average value of neutrophil, lymphocyte and NLR among pulmonary TB with no cavitation, with cavitation and with HIV co-infection.

	Pulmonary TB			TB/HIV (n=27)	p-value*	p-value**
	No Cavitation (n=50)	With Cavitation (n=50)	Total (n=100)			
Neutrophils[a] (x10^3/µL)	6.61±1.40	8.27±1.45	7.4±1.45	5.14±2.19	0.004*	0.003*
Limphocytes[b] (x10^3/µL)	1.63±0.66	1.51±0.61	1.57±0.64	1.02±0.57	0.344	0.001*
NLR	4.42±1.86	5.98±1.85	5.16±1.88	6.05±2.67	0.009*	0.041*

The value presented as geometric mean±SD. *comparison TB with no cavitation *vs.* with cavitation; **comparison TB total *vs.* TB/HIV; [a]normal neutrophils value (1.5-8.0); [b]normal lymphocyte value (0.8-5.0).

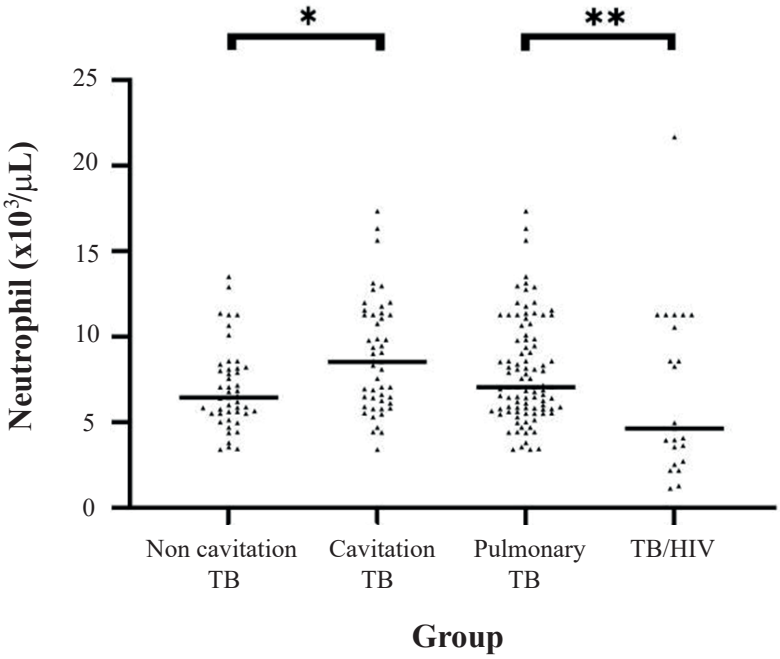

Figure 1. Neutrophil in pulmonary TB with no cavitation, with cavitation and with HIV co-infection. *TB with no cavitation *vs.* with cavitation (p=0.004); **pulmonary TB *vs*. TB/HIV (p=0.003).

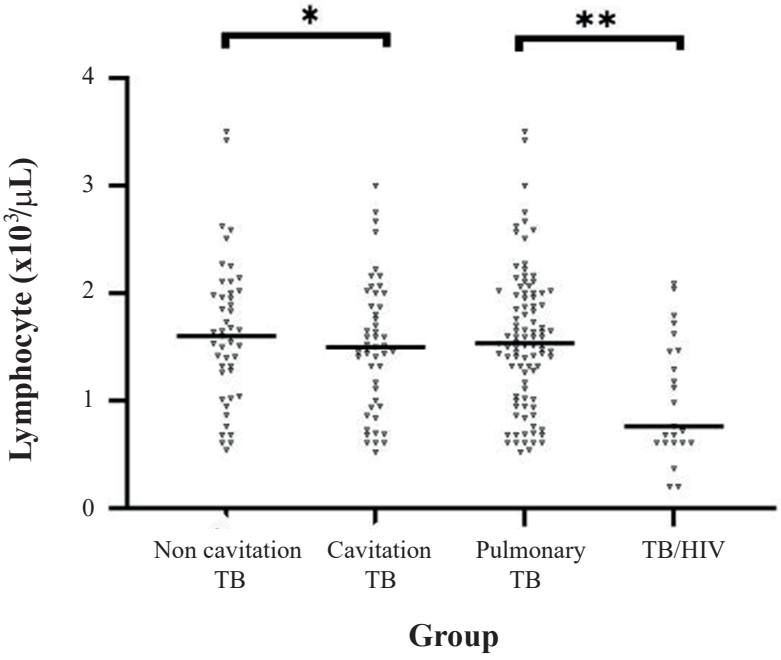

Figure 2. Lymphocyte in pulmonary TB with no cavitation, with cavitation and with HIV co-infection. *pulmonary TB with no cavitation *vs.* with cavitation (p=0.344); **pulmonary TB *vs.* TB/HIV (p=0.001).

Discussion

In this study, neutrophils, lymphocytes and the ratio of neutrophils over lymphocytes (NLR) have been compared among pulmonary TB with or without cavitation as well as with HIV co-infection. Previous study have shown that neutrophil, lymphocytes and NLR are well recognized as hematological parameters for identifying the active tuberculosis; predicting the risk of TB development, severity, recurrency; and monitoring response to antimicrobial therapy.(21) Evidence suggests that neutrophils play a role in both antimycobacterial activity and immunopathology during Mtb infection.(9) Our study has found that pulmonary TB with cavitation is significantly associated with increased neutrophils compared to pulmonary TB with no cavitation. In pulmonary TB, neutrophil is also significant increased compared to TB/

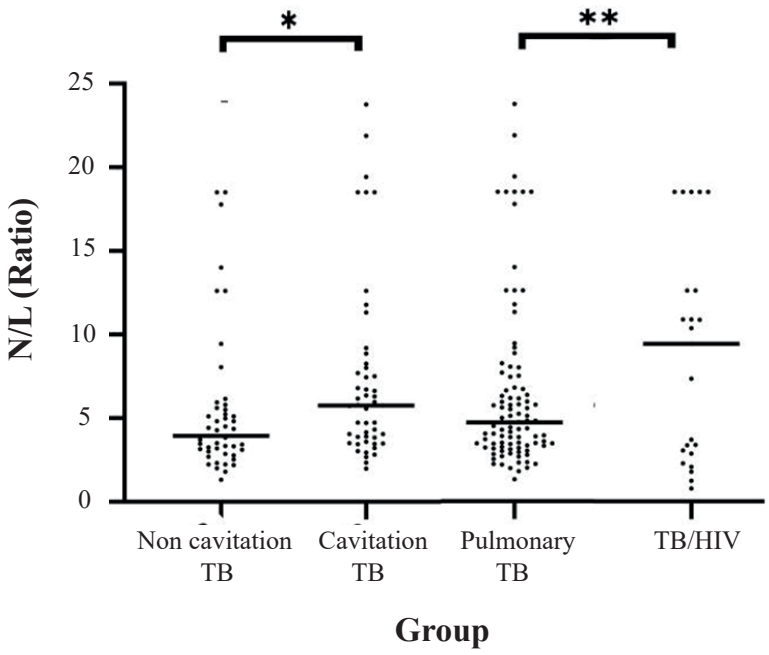

Figure 3. The ratio of neutrophil over lymphocyte (NLR) in pulmonary TB with no cavitation, with cavitation and with HIV co-infection. *pulmonary TB with no cavitation *vs.* with cavitation (p=0.009); **pulmonary TB *vs*. TB/HIV (p-0.041).

HIV. The increased neutrophil among all pulmonary TB is associated with dyspnea, night sweat, percentage of visible lung affected and cavitation.

Following infection, number of circulating neutrophils is increased while lymphocyte decreased.(20) In association with lymphocyte, we found among pulmonary TB and TB/HIV co-infection, lymphocytes are significantly decreased in TB/HIV co-infection as expected. Lymphocytopenia is associated with poor prognosis, whereas neutrophilia is recognized as an infectious marker.(20,22)

Combining both parameters as the ratio of neutrophils over lymphocytes (NLR), NLR has been used as an inflammatory marker to predict the severity of various diseases that can be easily obtained at low cost.(18,22) Inflammation plays a significant role in the pathogenesis of pulmonary TB. Previous study has found the correlation between higher NLR with advanced pulmonary TB.(18) Other study also reported a correlation of NLR with the severity of pulmonary TB.(18,22) High NLR seems to increase the likelihood of retreatment of pulmonary TB.(22)

Table 3. Comparison of neutrophils, lymphocytes and NLR in association with the clinical symptoms and X-ray findings.

Characteristics	Neutrophil[a]	*p*-value	Lymphocyte[b]	*p*-value	NLR[a]	*p*-value
Dyspnea						
Present	7.33	0.004*	1.6	0.69	5.04	0.076
Not Present	5.61		1.55		3.92	
Night Sweat						
Present	7.16	0.002*	1.58	0.76	4.92	0.04*
Not Present	4.78		1.55		3.46	
>60% Visible Lung Affected						
Present	7.83	0.041*	1.6	0.9	5.37	0.42
Not Present	6.33		1.59		4.28	
Consolidation						
Present	6.66	0.71	1.56	0.63	4.64	0.7
Not Present	6.7		1.62		4.45	
Cavitation						
Present	8.15	0.003*	1.57	0.29	5.6	0.004*
Not present	6.42		1.7		4.04	

[a]geometric mean; [b]mean; *statistical difference p<0.05.

In our study, NLR shows a significantly higher ratio among pulmonary TB patients with cavitation compared to non cavitation TB. Neutrophil products during Mtb infection such as neutrophil extracellular traps (NETs), gelatinases, ROS, and others make a cavity by degrading the extracellular matrix of lung tissue.(1) High oxygen concentration within the cavity gives a good environment for bacterial replication, leading to a large bacillary burden. (10) Large bacillary burden increase type-1 IFN that cause over activation of neutrophils then increase NLR among TB with cavitation.(23) Neutrophil acts like double edge sword in Mtb infection, it has antimicrobial activity in the granules but also has metalloproteinase that can damage the lung.

Neutrophil lymphocytes ratio among TB/HIV co-infection is significantly increased compared to pulmonary TB in this sudy. We somehow found lower number of circulatory lymphocyte count with relatively normal neutrophil count in TB/HIV coinfection groups. It probably explained the higher NLR but minimal lung affected in such patients. Unlike in pulmonary TB with cavity, neutrophilia in this group probably has significant role in facilitating lung damage. Previous study has explained that as a consequence of diminished numbers of $CD4^+$ T lymphocyte cells, patient with TB/HIV co-infection had decreased level of IFN-γ then increased neutrophil.(8,15) However, we didn't find such increasing number of neutrophils in TB/HIV groups. Other study also has proposed the use of the ratio of neutrophil over lymphocyte in peripheral blood as discriminating TB markers from non-TB infectious lung diseases.(21) Furthermore, to the best of our knowledge, this is the first study that has compared NLR value between TB and HIV co-infection. However, this study and previous study has not yet been clarified about correlation between high NLR value and poor outcome (22), therefore, further research is needed to clarify the relation of high NLR and poor prognosis.

Patient with TB/HIV-coinfection is associated with substantially higher mortality than patient with pulmonary TB only.(24) Our study has demonstrated that NLR among TB/HIV co-infection patient is significantly increased compared to pulmonary TB with or without cavitation. When pulmonary TB patients have very high NLR with low lymphocyte count these patients should be targeted for further HIV examination and follow up. An optimal management could potentially reduce the severity and associated mortality among TB patient with HIV co-infection. However, the cut-off value of high NLR associated with HIV co-infection need to be further explored.

This study has several limitations; with limited sample, measures lack of controlling possible confounders related to TB and HIV treatment, time of recruitment and prognostic indicators, it is difficult to judge the validity of the results. Therefore, it might be beneficial if additional study can present the research with consideration of power and bigger sample size. We also did not consider other opportunistic infections that might have affected neutrophil and lymphocyte counts, such as HBV co-infection (25) and plasmodium co-infection (26). Furthermore, HCV co-infection might also affect neutrophil counts.(27) Therefore, further studies excluding the effect of other infectious diseases is necessary to confirm this finding. As it is a cross-sectional study clinical research, this study also did not identify possible confounders at the recruitment phase such as the number of $CD4^+$ count, viral load, treatment types among TB/HIV co-infection patients: adjust the confounders statistically at the analysis phase to avoid possible bias.

Conclusion

Neutrophil is significantly higher among pulmonary TB patient with cavitation compared to TB patient without cavitation and TB/HIV co-infection. As expected, lymphocyte is significantly decreased among TB/HIV co-infection compared to pulmonary TB patient with or without cavitation, leading to a significantly higher NLR among TB/HIV co-infection compared to pulmonary TB patient. The high NLR in pulmonary TB with cavitation and HIV co-infection may be of great interest for biomarker in TB severity. Further study confirming NLR as potential marker is imperative

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Authors Contribution

BA and ES performed conceptualization, resources, methodology, supervision and writing - review and editing. RL managed biological samples. NS analyzed data, wrote the first draft of manuscript. All authors read and agreed with the contents and submission of this manuscript.

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