Analysis Of Systemic Immune-Inflammation Index (Sii) And Cd4 Count In Hiv/Aids Patients With And Without Tuberculosis Co-Infection

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Abstract.

Background: The Global Incidence Of Human Immunodeficiency Virus (Hiv) Infection Continues To Rise, With Increased Mortality Observed In The Presence Of Opportunistic Infections Such As Tuberculosis (Tb), Torch Infections (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex), And Candidiasis. The Systemic Immune-Inflammation Index (Sii), Derived From Neutrophil, Lymphocyte, And Platelet Counts Obtained Through Routine Complete Blood Count Testing, Has Recently Been Explored As A Potential Marker Of Immune Response And Inflammation In Hiv Patients, Particularly In Those With Tb Co-Infection. Objectives: To Analyze The Sii Index And Cd4 Count In Hiv Patients With And Without Tb Co-Infection. Methods: This Retrospective Study Analyzed Secondary Data From Hiv-Infected Patients Treated At Wahidin Sudirohusodo Hospital, Makassar, Between January 2022 And June 2024. The Mann–Whitney U Test Was Used To Compare Sii And Cd4 Counts Between Groups, And Receiver Operating Characteristic (Roc) Curve Analysis Was Performed To Assess The Predictive Value Of Sii For Tb Co-Infection. Results: Among 144 Patients, Sii Values Were Significantly Higher In The Hiv-Tb Co-Infection Group Compared To The Non-Tb Group (P = 0.001). Roc Analysis Revealed That An Sii Cut-Off Value Of 562.3 Yielded A Sensitivity Of 82.4% And A Specificity Of 35.5%, With An Area Under The Curve (Auc) Of 0.661, Indicating Weak Discriminatory Power. Cd4+ T Cell Counts Were Significantly Lower In Patients With Tb Co-Infection (P < 0.001). Conclusion: Sii Was Significantly Elevated In Hiv Patients With Tb Co-Infection, Demonstrating Relatively High Sensitivity And Suggesting Its Potential Utility As A Screening Tool For Identifying Tb Co-Infection In Hiv-Infected Individuals. Cd4+ T Cell Counts Were Also Significantly Lower In The Co-Infection Group, Consistent With Greater Immunosuppression.

Keywords: *Hiv; Aids; Tuberculosis; Cd4; Systemic Immune-Inflammation Index; Co-Infection and Opportunistic Infection.*

I. INTRODUCTION

Human Immunodeficiency Virus (HIV) is retrovirus that infects T lymphocytes and leads to progressive immunosuppression, culminating in a clinical syndrome known as Acquired Immune Deficiency Syndrome (AIDS). HIV impairs the immune response by reducing the number of CD4+ T cells. The rate of CD4+ cell destruction exceeds the cell regeneration resulting in immune system decline, which predisposes patients to AIDS and a wide range of systemic opportunistic infections[1] Among these opportunistic infections, tuberculosis (TB) caused by *Mycobacterium tuberculosis*, is the most common in AIDS patients[2] The risk of developing TB is 15–21 times higher in people living with HIV and represents a leading cause of morbidity and mortality in this population[3] Globally the incidence of HIV infection continues to rise, accompanied by increased mortality rates due to opportunistic infections such as TB, TORCH infections (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex), and candidiasis. Indonesia ranks second worldwide for TB burden, reporting approximately 845,000 cases in 2019, including 19,000 cases of TB-HIV co-infection[4] According to the Indonesian Ministry of Health as of 2020, 543,100 of the country's 271 million population were living with HIV, and an estimated 4,700 individuals with TB-HIV co-infection died. The World Health Organization (WHO) therefore recommends active TB screening in people living with HIV (PLHIV) as a key public health priority.

[3–5] According to the 2020 National Guidelines for Medical Services issued by the Indonesian Ministry of Health, the diagnosis of TB in PLHIV should be confirmed through bacteriological examinations such as the Rapid Molecular Test (RMT), acid-fast bacilli (AFB) smear microscopy, or culture. In cases with negative bacteriological results, a chest X-ray should be performed. If radiographic findings are suggestive of TB, a clinical diagnosis can be made. However, TB diagnosis in HIV-infected individuals presents several challenges. AFB smear microscopy using sputum samples often yields negative results, RMT is not universally available, and culture methods are time-consuming.[6] Delayed TB diagnosis in PLHIV is a major

contributor to the high mortality rate in this population1[3]HIV specifically targets and depletes CD4+ T cells, leading to compromised immune function and increased vulnerability to opportunistic and malignant infections. Monitoring CD4+ cell counts in HIV patients is crucial as it reflects immune status, tracks disease progression, and helps evaluate the response to antiretroviral therapy[6] A CD4+ count below 200 cells/mm³ significantly increases the risk of opportunistic infections[7]

WHO data from 2021 indicate that access to CD4 testing remains limited in many countries worldwide[3]A study by Widyaningrum et al. reported that 97% of HIV patients with tuberculosis (TB) co-infection had CD4 counts below 200 cells/mm³.[7] Similarly, a study by Yogi et al. found that the mean CD4 count was significantly lower in HIV patients with severe co-infections, such as disseminated TB (35.5 cells/mm³), compared to those with pulmonary TB (95.5 cells/mm³) or extrapulmonary TB (108 cells/mm³).[8] Recent research has evaluated the systemic immune-inflammation index (SII), which reflects the interaction between systemic inflammation and immune status. The SII is calculated using the formula: neutrophil count × platelet count / lymphocyte count, and can be obtained from a complete blood count.[9] Compared to single inflammatory markers, SII offers a more comprehensive evaluation of inflammatory and immune responses. This parameter is inexpensive, rapid, and widely accessible in most healthcare settings. SII, derived from peripheral blood cell counts, has been the subject of growing research interest in recent years.[10]Previous studies have investigated the use of SII in HIV patients as a predictor for conditions such as hypertension and cardiovascular disease.[11] However to date, no study has assessed the utility of SII in HIV-infected individuals in relation to tuberculosis co-infection.

II. METHODS

We conducted a retrospective study using secondary data from the medical records of patients aged ≥18 years who were diagnosed with HIV, with or without tuberculosis (TB) co-infection, at Wahidin Sudirohusodo Hospital, Makassar, between January 2022 and June 2024. CD4 counts and complete blood count (CBC) results obtained from medical records were used to calculate the systemic immune-inflammation index (SII).HIV diagnosis was confirmed based on the attending physician's assessment using either the Chemiluminescent Microparticle Immunoassay (CMIA) or Immunochromatographic Test (ICT). TB screening was performed through clinical evaluation, bacteriological tests (Rapid Molecular Test, acid-fast bacilli smear, or culture), and radiological imaging.

Patients with a positive TB result were categorized as HIV patients with TB co-infection. Those with negative TB findings and no other systemic infections were categorized as HIV patients without co-infection. Patients with a history of hematologic or oncologic diseases, systemic co-infections other than TB, or incomplete medical records were excluded from the study. The study population was divided into two groups: HIV/AIDS patients with TB co-infection and those without TB co-infection. The SII and CD4 counts were analyzed using SPSS version 27. Data normality was assessed using the Kolmogorov–Smirnov test. Comparisons between groups were analyzed using the Mann–Whitney U test. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of SII in distinguishing between HIV patients with and without TB co-infection. A p-value < 0.005 was considered statistically significant.

III. RESULT AND DISCUSSION

Result

A total of 144 research subjects met the inclusion criteria, consisting of 112 (77.8%) males and 32 (22.2%) females. The age range of the patients was 16 to 65 years, with a mean age of 34 ± 9 years. In the group of HIV patients with tuberculosis (TB) co-infection, 46 (92%) were male and 5 (9.8%) were female. Among HIV patients without TB co-infection, 66 (71%) were male and 27 (29%) were female. These characteristics are summarized in Table 1.

Table 1. Characteristics of the research subject

Characteristic	n (%)	Mean ± SD	Median (Min-Max)
Age (years)		34 ± 9	33 (16-65)

Gender	
Man	112 (77.8%)
Woman	32 (22.8%)
HIV with tuberculosis coinfection	51 (35.4%)
HIV without tuberculosis co-infection	93 (64.6%)

Normality testing with the Kolmogorov-Smirnov test revealed that sex, age, SII, and CD4 count were not normally distributed. As a result, additional analysis was performed using the Mann-Whitney U test, with the findings shown in Table 2. HIV patients with TB co-infection had a considerably lower mean lymphocyte count than those without co-infection. The mean leukocyte, neutrophil, and platelet counts were greater in the TB co-infection group, but the difference was not statistically significant ($p > 0.05$). The mean SII was considerably greater in HIV patients with TB co-infection. HIV patients with TB co-infection had considerably lower mean CD4 counts than those without ($p < 0.001$).

Table 2. Comparison of Laboratory Parameters Between HIV patients with and without tuberculosis co-infection

	HIV Co-infection Tuberculosis (n=51)	**HIV Without Tuberculosis Coinfection (n=93)**	**P* value**
Age (years)	35 ± 8	33 ± 9	0.297
Gender			
Man	46 (92%)	66 (71%)	0.008
Woman	5 (8%)	27 (29%)	
Leukocytes (cells/µl)	8,170 ± 4,220	7,940 ± 3,122	0.721
Neutrophils (cells/µl)	5,541 ± 2,944	5,121 ± 2,875	0.310
Lymphocytes (cells/µl)	1,550 ± 1,906	1,885 ± 870	<0.001
Platelets (103cells/µl)	301 ± 147	293 ± 99	0.838
SII	1,902 ± 2075	1,034 ± 1,098	0.001
Number of CD4 (cells/µl)	145 ± 129	314 ± 259	<0.001

**Mann-Whitney Test*

Based on the Receiver Operating Characteristics (ROC) curve analysis, the SII was found to be a statistically significant predictor of tuberculosis (TB) coinfection in HIV-infected patients, with an Area Under the Curve (AUC) of 0.661 (95% CI: 0.562-0.760, $p = 0.001$). A cut-off value of 562.3 for the SII resulted in a sensitivity of 82.4% and a specificity of 35.5%, according to Table 3 and Figure 1.

Table 3. Curve analysis *Receiver Operating Characeristics* (ROC) and SII predictive accuracy in people with HIV co-infection with tuberculosis

Variable	**AUC**	**95% CI**	**P value**	***Cut-off***	**Sensitivity (%)**	**Specificity (%)**
SII	0.661	0.562-0.760	0.001	562.3	82.4	35.5

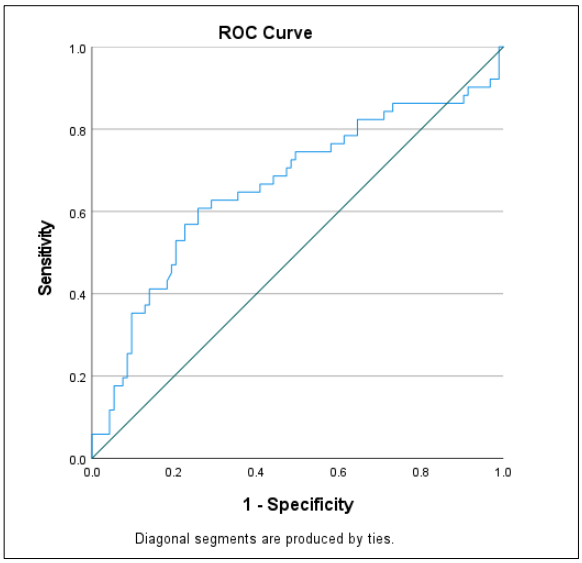

Fig 1. SII ROC curve in HIV tuberculosis coinfection

Discussion

This study featured 144 participants, with men outnumbering women in both groups. This data is consistent with the 2018 Indonesian Basic Health Research (Riskesdas) and the 2022 Tuberculosis Control Program Report, which both show a greater prevalence of tuberculosis among males in Indonesia. The mean age of the HIV-infected patients was 33 years, and those without TB coinfection were younger than those with TB coinfection.The Mann-Whitney test found that SII levels were considerably greater in HIV-infected patients with TB coinfection than those without (p = 0.001). This indicates a significant variation in systemic immune inflammatory status between the two groups. Elevated SII indicates increasing neutrophil and platelet counts while decreasing lymphocyte numbers, which is frequent in HIV patients with TB coinfection. Neutrophils have an important role in the innate immune response to Mycobacterium tuberculosis coinfection.[12] To control the infection and prevent bacterial multiplication, the human immune system forms granulomas made up of macrophages, lymphocytes, and neutrophils. Miyahara et al. have previously showed that neutrophils play a dual function in antimicrobial defence and immunopathological responses during M. tuberculosis infection.[13] Neutrophil-derived products, including neutrophil extracellular traps (NETs), gelatinase, and reactive oxygen species (ROS), cause lung tissue injury by dissolving the extracellular matrix and producing cavities. Lymphopenia is commonly observed in HIV infection caused by viral targeting and CD4+ T cell inactivation.

During HIV infection, circulating CD4+ lymphocyte counts can drop by 20-40%, explaining the considerable decrease in both lymphocyte and CD4+ T cell counts in HIV patients with TB coinfection.[12] Secondary thrombocytosis in tuberculosis patients has also been described, and it is thought to be connected with persistent inflammation. This syndrome is associated with high levels of platelet-derived growth factor (PDGF) and platelet factor 4.[14] The Systemic Immune-Inflammation Index's Receiver Operating Characteristic (ROC) curve study revealed a statistically significant Area Under the Curve (AUC) of 0.661 (p = 0.001). These data suggest that SII has limited discriminatory value as a predictor of tuberculosis (TB) coinfection in HIV patients. An SII cut-off value of 562.3 resulted in a sensitivity of 82.4%; however, the low specificity (35.5%) indicates a large incidence of false-positive results.This study has several limitations. As a retrospective analysis, it was unable to account for a variety of confounding factors that may affect immune function and susceptibility to opportunistic infections, particularly tuberculosis. Key characteristics like the stage of HIV infection and the severity of TB coinfection were not assessed, which may affect the interpretation of the findings.

IV. CONCLUSIONS

The findings demonstrated a significant difference in the SII between HIV-infected patients with and without tuberculosis (TB) coinfection, with higher SII values observed in the TB coinfection group. CD4+ T cell counts were significantly lower in HIV patients with TB coinfection compared to those without. Further studies are warranted to investigate the association between SII, the clinical stage of HIV infection, and the severity of TB coinfection.

REFERENCES

[1] Akiria Santi, A., & Sukarni, S. (2023). The Effectiveness Of Using Corsets On Reducing Pain Scale In Post SC Patients At Eka Hospital, South Tangerang In 2022. ***International Journal of Health and Pharmaceutical (IJHP)***, *3*(4), 677–682. https://doi.org/10.51601/ijhp.v3i4.225

[2] Laia, O. ., Lestari Nasution, S. ., & Ginting, . J. . (2023). Evaluation Of The Implementation Of Primary Care (P-Care) Application At Puskesmas Onolalu Nias Selatan In 2022. ***International Journal of Health and Pharmaceutical (IJHP)***, 3(4), 629–636. https://doi.org/10.51601/ijhp.v3i4.224

[3] Duha, K. B., Lestari Ramadhani Nasution, S. ., Girsang, E. ., & Suyono, T. . (2022). Analysis of Efficiency Of KDT-OAT and Removal Preparations on The Recovery of Pulmonary Tuberculosis. ***International Journal of Health and Pharmaceutical (IJHP)***, *2*(2), 284–289. https://doi.org/10.51601/ijhp.v2i2.43

[4] Rachmi Yuana, S., Girsang, E. ., & Ginting, . L. . (2023). Analysis Of The Influence Of Leader Behavior And Public Health Center Management Processes On Immunization Program Performance At Kuala Bali Public Health Center, Serdang Bedagai. ***International Journal of Health and Pharmaceutical (IJHP)***, 3(4), 594–601.

[5] Noni Rokaya Pasaribu, Ermi Girsang, Sri Lestari Ramadhani Nasution, & Chrismis Novalinda Ginting. (2022). Evaluation Of Planning And Implementation Occupational Safety And Health In Hospital Embung Fatimah Batam In 2021. ***International Journal of Health and Pharmaceutical (IJHP)***, *2*(2), 225–232.

[6] Zou S, Tan Y, Xiang Y, Liu Y, Zhu Q, Wu S, et al. The Role of CD4+CD8+ T Cells in HIV Infection With Tuberculosis. Front Public Heal. 2022; 10(May):1–10.

[7] WHO. Identifying common opportunistic infections among people with advanced HIV disease. In: Policy brief [Internet]. 2023. pp. 1–28. Available from: https://www.who.int/publications/i/item/9789240084957

[8] Ministry of Health of the Republic of Indonesia. National Action Plan for TB-HIV Collaboration 2020-2024 [Internet]. Ministry of Health of the Republic of Indonesia; 2021. 1 p. Available from: https://tbindonesia.or.id/wp-content/uploads/2022/09/RAN-Kolaborasi-TB-HIV-2020-2024.pdf

[9] Kerget B, Afşin DE, Aksakal A. The role of systemic immune-inflammation index (SII) in the differential diagnosis of granulomatous and reactive LAP diagnosed by endobronchial ultrasonography. Sarcoidosis Vasc Diffus Lung Dis. 2023; 40(3).

[10] Afriana N, Luhukay L, Mulyani PS, Irmawati, Romauli, Pratono, et al. HIV AIDS Annual Report 2022. In: Ministry of Health of the Republic of Indonesia [Internet]. 2023. pp. 1–91. Available from: http://p2p.kemkes.go.id/wp-content/uploads/2023/06/FINAL_6072023_Layout_HIVAIDS-1.pdf

[11] RI K. National Guidelines for HIV Management Medical Services. Decision of the Minister of Health of the Republic of Indonesia [Internet]. 2020.

[12] Widyaningrum LN, Indriati DW, Diyantoro, Sundari AS. Profile of Hiv/Aids Patients Coinfected With Tuberculosis in Ibnu Sina District Hospital, Gresik,East Java, Indonesia. ***J Vocat Heal Stud***. 2022; 6(2):102–6.

[13] P DY, Dian S D, Gayatri AY, Utama MS, Somia A, Parwati M T. Characteristics of HIV/AIDS patients with tuberculosis coinfection at the VCT polyclinic of Sanglah Hospital. Medicina (B Aires). 2019; 50(2):386–90.

[14] Ştefanescu S, Cocoş R, Turcu-Stiolica A, Mahler B, Meca AD, Giura AMC, et al. Evaluation of prognostic significance of hematological profiles after the intensive phase treatment in pulmonary tuberculosis patients from Romania. Eval Progn significance Hematol profiles after intensive phase Treat Pulm Tuberc patients from Rom. 2021; 16 (4 April): 1–18.

[15] He X, Lin Y, Qiu H, Wang X, Zhu B. Predictive effect of systemic immune inflammatory index combined with neutrophil-to-lymphocyte ratio on prognosis of patients with acute-on-chronic liver failure. 2023;15(12):6841–8.

[16] Ou-Yang H, Fu HY, Luo Y, Xu ZY, Liu J, Gao R, et al. Inflammation markers and the risk of hypertension in people living with HIV. Front Immunol. 2023; 14(March):1–11.

[17] Sulastri N, Alisjahbana B, Livia R, Sahiratmadja E. Higher Neutrophil-lymphocyte Ratio in TB/HIV Co-infection Compared to Pulmonary Tuberculosis. ***Indones Biomed J***. 2021; 13(4):375–82.

[18] Azevedo-Pereira JM, Pires D, Calado M, Mandal M, Santos-Costa Q, Anes E. HIV/Mtb Co-Infection: From the Amplification of Disease Pathogenesis to an "Emerging Syndemic." Microorganisms. 2023; 11(4):1–18.

[19] Vohra P, Nimonkar S, Belkhode V, Potdar S, Bhanot R, Izna, et al. CD4 cells count as a Prognostic Marker in HIV Patients with Comparative Analysis of Various Studies in Asia Pacific Region. ***J Fam Med Prim Care*** [Internet]. 2020; 6(2):2431–6.