IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 4 | Issue: 2 | Mar – Apr 2023 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v4i2.3

Correlation Between CD4, Hemoglobin, and Body Mass Index Levels on The Success of Intensive Phase Therapy among Positive Bacteriological Tuberculosis Patients with Human Immunodeficiency Virus Co-infection

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ABSTRACT

Background: Tuberculosis and HIV infections are still a combination of diseases with high mortality rates. The success of intensive phase therapy of positive bacteriological TB patients with HIV co-infection can reduce morbidity and mortality rates. This study aims to determine the relationship between CD4 levels, HB, and BMI on the success of intensive phase therapy among positive bacteriological TB patients with HIV co-infection. ***Method:*** This research was an observational analytic study using a retrospective cohort study design conducted in Bali over 5 years (January 2016 to December 2021). Of 120 subjects, 118 subjects met the research requirements. The data was analyzed by Univariate analysis, Bivariate analysis was carried out using Chi-Square, and multivariate analysis was performed using multiple logistic regression. ***Results:*** a significant correlation was found between CD4 levels (RR=3,03, p= 0,004), HB (RR= 1,92, p= 0,006), BMI (RR= 5,91 p< 0,001) with successful intensive phase therapy in Bacteriologically Confirmed TB patients with HIV co-infection. All independent variables simultaneously affected sputum conversion (p<0,001; R Square = 0,479; CI: 95%). This study also found that BMI was the dominant predictor that affected the success of intensive phase therapy in Bacteriologically Confirmed TB patients with HIV co-infection (p<0,001; OR: 5,193; CI 95%). ***Conclusion***: CD4, HB, and BMI levels are significantly related to the success of intensive phase therapy in Bacteriologically Confirmed TB patients with HIV co-infection.

Keywords: Body Mass Index (BMI); CD4; Hemoglobin (HB); Human immunodeficiency virus (HIV); Tuberculosis (TB)

INTRODUCTION

TB (Tuberculosis) and HIV (Human Immunodeficiency Virus) infections are still considered the disease' combination with high mortality rates. Thus, it affects one another in every aspect, including pathogenesis, epidemiology, clinical manifestations, treatment, and prevention. HIV-positive people are estimated to be 21-34 times more prone to active TB. In addition, TB was also the leading cause of death in 40% of HIV-positive patients in 2016. During the same year in Indonesia, 360,565 TB cases were found, with 14% known to also suffer from HIV-positive [1].

Several factors play a significant role in the occurrence of the TB-HIV co-infection. CD4+ is essential in the early days of diagnosis and treatment with antiretroviral treatment (ART), which confirms CD4+ levels alleviation [2].

Ease regarding the CD4 levels could lead to a progressive decline in the immune system, relief of TCD4 lymphocyte cells, and the inability to control opportunistic infections. It also causes cellular response failure at M.TB's predilection to cite and induces the M.TB activation, which causes an increase in the number of germs and affects the sputum conversion [3].

In addition to CD4, the patient's hemoglobin (HB) also plays a significant role. The presence of anemia in chronic infections, including TB, is believed to occur due to the low immune system response. The cells release cytokines that affect recovery and defense body mechanisms against diseases. The production of cytokines can also affect the body's functioning. Persistent anemia also led to sputum conversion failure [4].

The nutritional status contributes to the success of TB patients with HIV co-infection treatment as well. Malnutrition could increase the progressivity of pulmonary TB disease. In the same way, the disease causes poor nutritional status [5]. This combination of infections also results in a lack of protein energy characterized by decreased muscle mass and fat (*wasting*) [6]. It could worsen the progressivity of HIV infection by lowering the immune system and lead the chance of opportunistic infections.

This study aims to determine the correlation between CD4, HB, and BMI levels with the success of intensive phase therapy in bacteriologically confirmed TB patients with HIV co-infection.

MATERIALS AND METHODS

Research Design

An observational analytical study was employed by using a retrospective cohort study design in 61 TB bacteriologically confirmed patients with HIV co-infection over 5 years period (January 2016 until December 2021). The research was conducted at Prof IGNG Ngoerah General Hospital. The samples were taken using *a consecutive non-probability* sampling technique and employed inclusion and exclusion criteria.

Data Analysis

The data was carried out by performing statistical analysis using computerized programs and presented in the form of textual tables and graphs. Bivariate analysis is employed by calculating relative risk from the C-Square test. The data were then analyzed by Multivariate analysis with *an* omnibus test of the coefficient model to analyze simultaneous relationships and logistic regression used to see the size of risk ratio (RR) associations.

Ethical consideration

Informed consent was not obtained because we used secondary data. The Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, approved the study ethic approval through the ethical clearance certificate No. 2679/UN14.2.2.VII.14/LT/2021 This approval ensured the study was conducted responsibly and ethically accountable.

RESULTS

Our study analyzed the demographic characteristics of the research subjects (Table 1), BMI and laboratory Examination (Table 2), the correlation between CD4, HB, BMI to Sputum Conversion (Table 3), simultaneous test analysis (Table 4), and Logistic Regression test Analysis (Table 5).

TABLE 1: Demographic Characteristics Of Research Subjects.

Variable	n=118	Percentage (%)
Age (Mean± Sd, Min-Max, Range)	(38.36 ± 9.64, 23 - 72, 49)	
17 – 25 YO	8	6,8
26 – 35 YO	47	39,8
36 – 45 YO	37	31,4
46 – 55 YO	20	16,9
56 – 65 YO	5	4,2
> 65 YO	1	0.8
Gender		
Man	92	78,0
Woman	26	22,0
Education		
Elementary School	6	5,1
Junior High School	8	6,8
Senior High School	62	52,5
Undergraduate	42	35,6
Work		
House Wife	7	5.9
Private Sectors	35	29.7
Entrepreneurial	36	30.5
Civil Servants-Pensioners	18	15.3
Independent Professional	19	16.1
Students	2	1.7
Not Working	1	0.8

TABLE 2: BMI and laboratory Examination among Research Subjects.

Variable	n=118	Percentage (%)
BMI (Mean± SD, Min-Max)	(18.70 ± 2.96, 11.43 – 27.85)	
Thin	58	49,2
Usual	60	50,8
HB level (Mean± SD, Min-Max)	(9.99 ± 2.15, 5 -16)	
Anemia	62	52,5
No Anemia	56	47,5
CD4 levels (mean± SD, min-max)	(124.11 ± 101.20, 1-53)	
< 200	92	78,0
≥ 200	26	22,0
BTA Month 2		
No Conversion	47	39,8
Conversion	71	60,2

TABLE 3: Relationship between CD4, HB, BMI to Sputum Conversion.

No	Variable	Sputum Conversion				*RR*	*Sig. p*
		No Conversion		Conversion			
		n	%	N	%		
		CD4 levels					
1	< 200	43	46,7	49	53,3	3,03	0,004
	≥ 200	4	15,4	22	84,6		
		HB					
2	Anemia	32	51,6	30	48,4	1,92	0,006
	No Anemia	15	26,8	41	73,2		
		BMI					
3	Under	40	69,0	18	31,0	5,91	< 0.001
	Normal	7	11,7	53	88,3		

TABLE 4: Results of simultaneous test analysis between research variables.

Variable	Sputum Conversion		
	Nagelkerke R Square	Cox & Snell R Square	Sig. p
CD4 < 200	0,479	0,354	< 0.001
Anemic			
Under-Normal BMI			

TABLE 5: Results of Logistic Regression test Analysis.

Variable	Sig. p	Adj RR (CI 95%)
CD4 < 200	0,332	1,689 (0.586-4.871)
Anemic	0,198	1,510 (0.806-2.827)
Under-normal BMI	0,000*	5,193 (2,299-11,729)

DISCUSSION

The subjects were predominantly male and similar to the previous findings [7–9]. This is supported by the latest primary health research data in Indonesia in 2018, which quoted that TB incidence tends to be more occurring in males due to the difference in social interactions, smoking behavior, and drinking alcohol that causes a decrease in the body's defense system which is the risk of TB [10]. In terms of age, most of the subjects were in the range 26-35 years which was similar to the previous findings [11] and was classified as a formative stage with a high level of mobility and social interaction that could be a source of TB transmission in the community [12]. The majority of the subjects had a high school level or equivalent, where the higher the level of education will be, the higher the individual's ability to receive and understand the health information received [13]. Regarding the jobs, most of them were entrepreneurs, which could be the risk of transmitting high interaction with other people [14].

The BMI among the study subjects was found in different values in the normal range. The nutritional status is essential and must be considered before and during the treatment period as they may significantly contribute to sputum conversion. The examination of laboratory parameters showed that most of them were evaluated in an anemic condition. Studies quoted that 3 mechanisms can cause anemia in HIV infection: an alleviation in erythrocyte production, an increase in erythrocyte digestion, and the ineffectiveness of erythrocyte production [15]. HIV and TB have a very significant relationship because HIV infection can increase the progressivity of TB cases and vice versa [16].

Our study has proven that CD4 levels < 200 increase the risk of the non-conversion phenomenon in bacteriologically confirmed TB patients with HIV co-infection. Our study found that patients with CD4 levels < 200 cells/mm 3 had a 3.03 times greater risk of unconverted sputum than the average CD4 level. Our findings are by previous theories and studies, which state that average CD4 values in bacteriologically confirmed TB patients with HIV co-infection play a significant role in the immunity factor. It could be a great chance of sputum conversion [17].

T-CD4 cells are the basis of a specific immune response to infections, especially intracellular pathogens. These cells are also the main targets of HIV. When HIV infects T-CD4 lymphocyte cells, there is a drastic alleviation in the number of T-CD4 lymphocyte cells. The virus that enters the T-CD4 lymphocyte cells will replicate, increase their number sharply, and destroy the cells by themselves.

The progressivity of HIV-related immunodeficiencies also correlated to the progressivity of host response failure in granuloma formation to M.Tb [18]. The immune response to M.Tb is complex by the role of the antimycobacterial response of the macrophages. M.Tb, which successfully survives the intracellular bactericidal mechanism, can replicate slowly in the intracellular environment of macrophages. The presentation of antigens to CD4 T cells, initiating the development of cell-mediated immune responses and slow-type hypersensitivity within 2-4 weeks after the initial onset of infection.

Macrophages secrete interleukin-12 (IL-12) to facilitate the clonal expansion of type 1 CD4 T-helper lymphocytes, which will produce gamma interferon (IFN-γ). IFNγ is a macrophages' potent activator, which promotes intracellular bactericidal mechanisms. The release of other chemokines, such as interleukin-8 (IL-8), and other proinflammation cytokines, such as tumor necrosis factor-α (TNF-α), facilitates the recruitment and activation of mononuclear cells respectfully [18].

The formation of granulomas limits infection from M.Tb. TB granulomas are characterized by activation and differentiation of macrophage epithelioid and the development of Langhans cells. CD4 T cells found in the peripheral part of the granuloma structure have an essential role in the immune response mediated by kaseosa necrosis cells that occur in the central region and inhibit the growth of extracellular bacteria. If the granuloma structure fails to limit M. tuberculosis infection, the kaseosa structure melts and causes rapid growth of extracellular mycobacteria. Furthermore, the spread of tissue damage and cavity formation causes clinical symptoms of active TB [19].

Another study also quoted that Treg Cells are elevated in patients with active diseases that can suppress the immune response, especially the interferon-gamma produced by Th1 cells. Treg cells which are CD4, can experience a significant elevation in the blood of TB patients. During TB infection, the anti-inflammatory cytokine IL-10 is produced by macrophages and T cells. During the infection, Treg can limit the accumulation of T cells in the lungs, thereby limiting subsequent effector responses. Interleukin 10 (IL-10) can inactivate macrophages, inhibiting the production of IL-12, which will also inhibit the production of IFN-γ. In addition, IL-10 directly inhibits the response of CD4+ T cells and inhibits the function of antigen-presenting cells (APCs) in cells infected with TB germs. IL-10 expression is associated with sputum conversion during antituberculosis drug therapy [20].

Our study also found that anemic conditions are confirmed as a factor that can increase the chances of sputum conversion. Our findings regarding the patients with anemia had a risk of unconverted sputum of 1.92 or 2 times greater than patients with normal hemoglobin. Various pathogenesis has been proposed to explain anemia in tuberculosis. However, most recent studies emphasize the impact of erythropoiesis by inflammatory mediators as the underlying factors contributing to anemia. This condition occurs due to the dysregulation of the immune system related to the systemic response to the disease condition suffered. The increase in pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and Interferon-γ affects the alleviation in progenitor erythroid. This alleviated inhibits the differentiation and proliferation of erythrocytes, respectively. The pathogenesis of anemia can be examined more deeply through the invasion pathways of microorganisms, malignant cells, or autoimmune reactions that cause activation of T cells (CD3+) and monocytes. These cells induce immune effector mechanisms by producing cytokines such as interferon-γ from T cells and TNF-α, Interleukin-1, Interleukin-6, and Interleukin-10 (from monocytes or macrophages) as it is known that the expression of IL-10 is associated with a decrease in the number of *Mycobacterium tuberculosis* bacteria and it affects the sputum conversion [20].

This study aligns with previous studies, which stated that low HB values have a higher risk of un-converted sputum [21,22]. Normal HB levels in this combination of diseases play a major role in the conversion process due to the significant role of OAT consumed [22].

In addition, another study quoted that people with pulmonary TB with anemic conditions have a risk of conversion failure after undergoing two months of treatment [21]. This statement is reinforced by other studies that state that anemia in tuberculosis patients can be fizzled out after OAT treatment [23] and quoted by a further related analysis [24].

The conversion failure in this study can be caused due to the presence of erythropoiesis suppression by inflammatory mediators, which is the most frequent pathogenesis of anemia that occurs in confirmed cases of TB. This condition causes the alleviation of the body's resistance which also alleviates the cellular immune response. The lower body's resistance is, the more inadequate the body is to the microorganism surface, and the conversion control needs to be achieved optimally [25].

To answer our third hypothesis, we found that lower BMI could signify the risk of sputum conversion failure among the research subjects. A patient who had lower BMI values was considered to have 5.91- or six times more significant trouble experiencing non-conversion. Common BMI values have been associated with increased patient mortality rates [26]. It is also related to patient malnutrition which increases the risk of TB by the inadequacy of the patient's immune system [27]. Therefore, it can affect the alleviation of drug concentration in the blood plasma and improve the kidneys' function to perform discharge. As a result, TB treatment's effectiveness is adequate and increases the risk of treatment failure, even expanding the risk of recurrence [14]. Our study found that most pulmonary TB patients who did not experience sputum conversion had a BMI of < 18.5 kg/m^2. Sputum Conversion failure is experienced due to the presence of OAT malabsorption [28].

Our findings are similar to previous studies that quoted patients with low BMI status had a higher risk of un-converted sputum [29–32]. Those studies are also in line with other studies that signified TB patients with malnutrition status resulting in the production of antibodies and lymphocytes inhibited and affected the healing process [33].

The occurrence of sputum conversion failure among patients with lower BMI also could be explained by the presence of nutritional deficiencies, which can affect endurance and immunity response in the patient's body. In addition, patients with a lower BMI tend to experience metabolic processes' changes in the body, such as increased catabolism to activate the work of the immune system, *anabolic block* occurs where amino acids cannot be built into a more complex protein arrangement which caused lacks of energy and reducing fat deposits in the body which impacted the cells and tissues, as well as an alleviation in the leptin hormone in the blood. Thus alleviating the patient's intake as well as the body's resistance [34]. This condition then causes the risk of sputum conversion's failure to become even more significant [35].

To extend our fourth hypothesis, we have found that all independent variables in this study have simultaneously influenced the success of intensive phase therapy in bacteriologically confirmed TB patients with HIV co-infection (*p value*<0.001; CI: 95%). We have obtained *Nagelkerke* R Square values of 0.479 and *Cox & Snell R Square* of 0.354, which showed that the ability of all independent variables to explain dependent variables is as significant as 0.479 or 47.9%, and there are 52.1% of other factors outside the model could describe the dependent variable.

It is known that CD4, HB, and BMI alike have a significant influence on sputum conversion among bacteriologically confirmed TB patients with HIV co-infection. However, BMI level was the dominant predictor in supporting the sputum conversion. Our findings are supported by previous studies that signified the BMI as the main predictor of sputum conversion [36–38]. BMI as the main predictor in influencing the sputum conversion among TB-coinfected HIV patients, is explained by several mechanisms. The low nutritional status of the patient affects the alleviation of drug concentration and improves the kidneys' function to perform disposal [39]. Malabsorption occurs due to morphological changes in the intestinal caused by malnutrition. This alteration causes a decrease in the activity of enzymes that help the absorption process, which affects TB treatment failure.

CONCLUSION

CD4, HB, and BMI levels were associated with the success of intensive phase therapy in bacteriologically confirmed TB patients with HIV co-infection by using sputum conversion as the gold standard. Further research needs to be conducted to identify the type of TB cases (new cases, long cases, or relapse) and analyze the other factors contributing to sputum conversion.

ACKNOWLEDGMENT

Researchers would like to thank Udayana University and Prof IGNG Ngoerah General Hospital, which permitted them to conduct this study.

CONFLICT OF INTEREST

The authors have no conflict of interest related to the study, authorship, and/or article publication to declare.

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