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CORRELATION BETWEEN ERYTHROCYTE INDEX LEVELS WITH THE ANEMIA MORPHOLOGY IN LEPROSY PATIENTS BEFORE THERAPY: A SECONDARY DATA RESEARCH

Marrietta Sugiarti Sadeli, Luh Made Mas Rusyati*, Ni Luh Putu Ratih Vibriyanti Karna
Dermatology and Venereology Department, Faculty of Medicine, Universitas Udayana, Jln P.B. Sudirman, Dangin Puri Klod, Denpasar Barat, Denpasar, Bali 80234, Indonesia
*rusyati@unud.ac.id

ABSTRACT
Leprosy is a chronic inflammatory disease caused by *Mycobacterium leprae*. Chronic infection can cause anemia of chronic disease which is characterized by normochromic normocytic morphology. This study was conducted to assess the relationship between erythrocyte index levels (MCV, MCH, and MCHC) with the morphology of anemia that occurs in leprosy patients before treatment. A cross-sectional study using secondary data from medical records and management information system applications at Sanglah Hospital. The variables of this study were age, sex, hemoglobin levels, and erythrocyte index levels (MCV, MCH, and MCHC). Data were collected after permission was granted and ethical clearance was completed. Of the 156 study samples, 106 patients were diagnosed with leprosy who had not received therapy and 50 patients were not leprosy. The mean age of the patients was 39.15 ± 12.218 years and male patients were more common than female patients. There was a positive correlation between anemia, normal erythrocyte index levels, and the leprosy group. Following are the p-values, prevalence ratios, and confidence intervals; anemia [p= 0.017; PR(95% CI)= 1,458(1.034-2.056)], MCV, MCH, and MCHC [p= 0.020; PR(95% CI)= 1,268(1.010-1.591); p= 0.015; PR(95% CI)= 1,293(1,021-1,639); p= 0.009; PR(95% CI)= 1,297(1,036-1,624)]. The results of the analysis were statistically significant and clinically important. Leprosy patients had anemia before therapy with normochromic normocytic anemia morphology in accordance with anemia of chronic disease.

Keywords: anemia; anemia morphology; erythrocyte index; leprosy

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INTRODUCTION

Leprosy is a chronic inflammatory disease caused by *Mycobacterium leprae*. Multiplication of *M. leprae* occurs more slowly than other bacteria so the course of the disease and clinical manifestations in leprosy is longer, varied, and chronic (Reilley-Luther et al., 2020).
Chronic infection with bacterial, viral, or fungal pathogens can cause anemia. Anemia is defined as a condition in which hemoglobin concentration and/or red blood cell numbers are lower than normal and insufficient to meet an individual's physiological needs (Salokhiddinovna, 2023).This occurs when the balance between blood loss and blood production is disturbed. Anemia that occurs due to chronic infection, inflammation, trauma, and neoplastic disease that lasts 1-2 months is known as anemia of chronic disease (ACD) (Chaparro & Suchdev, 2019). In addition, most cases of leprosy are in poor or developing countries with low socioeconomic conditions . This is related to malnutrition in leprosy patients, so it is often assumed that the anemia that occurs is iron deficiency anemia. Hemolytic anemia can also occur in patients with leprosy caused by the administration of multidrug therapy (MDT), namely dapsone.

Leprosy remains a health problem in Indonesia due to several provinces not having fully eliminated the disease. Leprosy imposes a burden on sufferers both physically and

mentally due to the stigma that affects the psychological condition of patients. Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae (M. leprae) (Setyawati et al., 2024). In 2019, 202.256 new cases of leprosy were detected in 118 countries, with Indonesia being one of the largest contributors. Data shows that 79% of cases come from India, Brazil, and Indonesia (Grossi et al., 2019). Chronic diseases, whether from bacterial infection or other causes, can lead to anemia. Anemia is characterized by a decrease in red blood cells or hemoglobin concentration below the normal range (Padmawijaya et al., 2022). According to Sadeli, anemia has a positive correlation with leprosy, indicating that anemia can occur in leprosy patients even before therapy, with normal erythrocyte indexpointing to anemia of chronic diseases (Agura, 2024). Anemia of chronic disease shows low reticulocytes, indicating a failure in reticulocyte production to compensate for the decreased red blood cells. Leukocyte and platelet counts follow the course of the underlying disease. Additionally, M. leprae require iron for increased pathogenicity, and the increased uptake and retention of iron due to the infection process reduce its availability for erythroid progenitor cell proliferation, disrupting red blood cell lifespan and leading to anemia (Chuang et al., 2023). This study aims to prove the relationship between erythrocyte index levels and the morphology of anemia that occurs in leprosy patients before therapy.

METHOD

The design of this study is a study using secondary data from medical records and the application of management information systems at Sanglah Hospital (SIMARS), with a cross-sectional study approach. The study was conducted at the Sanglah Central General Hospital (RSUP) Denpasar, Bali Province. Subjects are all new leprosy patients 18-65 years old, male or female who meet the diagnostic criteria, have never received MDT treatment, and have had a complete blood count listed in the SIMARS application in the period January 2018 to December 2021. Inclusion criteria for non-leprosy patients in this study were subjects who were not leprosy patients who visited the Dermatology and Venereology Polyclinic, Sanglah Hospital, Denpasar, and had a complete blood count as listed in the SIMARS application. Exclusion criteria include incomplete data, having received MDT treatment or release from treatment, smoker, pregnant, having or are suffering from diseases such as chronic kidney failure, rheumatoid arthritis, systemic lupus erythematosus, malignancy or neoplasia, liver cirrhosis, blood disorders (sickle cell anemia, thalassemia), bone marrow disorders, chronic bleeding due to gastrointestinal disorders, have or are suffering from vitamin B12 and/or folate deficiency. The data have been rechecked from medical records and SIMARS to reduce the possibility of bias.

The variables of this study were age, sex, hemoglobin levels, and erythrocyte index levels (MCV, MCH, and MCHC). Secondary data were collected from medical records and blood laboratory results through the SIMARS application for leprosy patients before receiving therapy in the period January 2018 to December 2021. This study used a total sampling method and we collected 208 samples. Of those, only 156 pass the criteria and be included. Data were tabulated and analyzed using SPSS 26. Quantitative data were expressed in mean ± standard deviation while qualitative data were expressed in numbers and percentages. Kolmogorov–Smirnov test was used to show whether the data were normally distributed. An unpaired T-test was used for comparative analysis. Pearson's Chi-square test was used for bivariate analysis. A p-value <0.05 was considered statistically significant. This study received ethics approval from the Ethics Committee of the Faculty of Medicine, Udayana University/ Sanglah General Hospital with approval number 2525/UN14.2.2.VII.14/LT/2021.

RESULT

This study involved secondary data from leprosy patients and non-leprosy patients with a ratio of 2.3: 1. A total of 156 patients met the inclusion criteria, and 52 patients met the exclusion criteria. Of these 156 patients, 106 patients were diagnosed with leprosy, and 50 were not leprosy. The characteristics of the research subjects can be seen in Table 1. The comparison analysis of the mean age in the two groups was analyzed using an unpaired T-test because the data were normally distributed. In this analysis, there was no significant difference in the mean age between the leprosy group and the non-leprosy group ($p<0.05$).

A bivariate analysis result using Chi-Square test is shown in Table 2. We found a positive correlation between anemia and the leprosy group ($p = 0.017$; RP = 1.458). The leprosy group had a risk of 1,458 times more likely to develop anemia than the non-leprosy group. The positive correlation also found between MCV and the leprosy group ($p= 0.020$; RP= 1.268). The leprosy group had a risk of 1,268 times more likely to have normal MCV levels than the non-leprosy group. The MCH and MCHC also shown positive correlation with leprosy group ($p= 0.015$; RP= 1.293 and $p= 0.009$; RP= 1.297, respectively). The leprosy group had a risk of 1,293 times and 1,297 times more likely to have normal MCH and MCHC levels than the non-leprosy group.

Table 1.
Characteristics of research subjects

Characteristics	Group f (%), mean ± SD		P value
	Leprosy (n=106)	Non-Leprosy (n=50)	
Sex			
Male	63 (59,4)	28 (56,0)	0,685
Female	43 (40,6)	22 (44,0)	
Marital status			
Single	20 (18,9)	9 (18,0)	0.897
Married	86 (81,1)	41 (82,0)	
Education status			
No education – Junior high school	10 (9,4)	5 (10,0)	0,129
Senior high school	58 (54,7)	19 (38,0)	
Bachelor and above	38 (35,8)	26 (52,0)	
Domicile			
Denpasar	40 (37,7)	19 (38,0)	0,149
Badung	34 (32,1)	6 (12,0)	
Tabanan	1 (0,9)	3 (6,0)	
Buleleng	7 (6,6)	3 (6,0)	
Gianyar	3 (2,8)	3 (6,0)	
Karangasem	5 (4,7)	6 (12,0)	
Klungkung	2 (1,9)	1 (2,0)	
Jembrana	3 (2,8)	1 (2,0)	
Bangli	2 (1,9)	2 (4,0)	
Outside Bali	9 (8,5)	6 (12,0)	
Age (year)	39,15 ± 12,218	42,52 ± 14,403	0,157
Hemoglobin levels			
Anemia	68 (64,2)	22 (44,0)	0,017*
No Anemia	38 (35,8)	28 (56,0)	
Erythrocyte Index Level			
MCV			
Normal	86 (81,1)	32 (64,0)	0,020*
Low	20 (18,9)	18 (36,0)	
MCH			0,015*
Normal	85 (80,2)	31 (62,0)	
Low	21 (19,8)	19 (38,0)	
MCHC			0,009*
Normal	88 (83,0)	32 (64,0)	
Low	18 (17,0)	18 (36,0)	

*Significantly different if p<0.05; SB: standard deviation; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration

Table 2.
Bivariate Analysis in the Leprosy and the Non-Leprosy Group

Variable	Leprosy	Non-Leprosy	PR (CI95%)	P value
Anemia	68 (64,2)	22 (44,0)	1,458 (1,034-2,056)	0,017*
No anemia	38 (35,8)	28 (56,0)		
MCV normal	86 (81,1)	32 (64,0)	1,268 (1,010-1,591)	0,020*
MCV low	20 (18,9)	18 (36,0)		
MCH normal	85 (80,2)	31 (62,0)	1,293 (1,021-1,639)	0,015*
MCH low	21 (19,8)	19 (38,0)		
MCHC normal	88 (83,0)	32 (64,0)	1,297 (1,036-1,624)	0,009*
MCHC low	18 (17,0)	18 (36,0)		

*Significant if p<0.05; analysis with Chi Square test. PR: Prevalence Ratio; CI: Confidence Interval

Table 3.
STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2-3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2-3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	3
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	-

	Item No	Recommendation	Page No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3,7
		(b) Indicate number of participants with missing data for each variable of interest	3
Outcome data	15*	Report numbers of outcome events or summary measures	3,4,9,10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	3,4,9,10
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	4
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	4,5
Generalisability	21	Discuss the generalisability (external validity) of the study results	4,5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for exposed and unexposed groups

DISCUSSION

From existing studies, gender-related differences existed among leprosy cases, and female patients tend to be younger than males. In most Asian countries, leprosy affects men more than women, while in Africa, female patients outnumber males (Liu et al., 2018). Leprosy can also occur in all age groups, influenced by socioeconomic, and the incidence of leprosy is said to be lower at high socioeconomic levels (Nery et al., 2019). From previous studies, the lower the socioeconomic status, the more severe the disease will be, and vice versa (Balgomera et al., 2024).

The findings in this study are in accordance with existing studies, there are more men than women in the leprosy group who have not received therapy with an average age according to the age of young and productive adults (de Oliveira et al., 2020). The results of the above study are in accordance with the findings in this study, most leprosy patients have normal erythrocyte index levels of MCV, MCH, and MCHC which indicate the morphology of the anemia that occurs is normochromic normocytic. The normochromic normocytic morphology is commonly associated with anemia of chronic disease (Pepito et al., 2023).

Anemia of chronic disease is generally described as normochromic normocytic anemia but can become hypochromic microcytic anemia if the underlying disease becomes more progressive (Chase et al., 2023). Another study described cases of anemia of severe chronic disease, severe anemia may occur with microcytic hypochromic morphology in about 37.5% of cases (Simbauranga et al., 2015). These findings may be due to severe anemia in severe chronic disease anemia or to progressively progressive underlying disease, iron deficiency anemia, and/or hemolytic anemia. The limitation of this study is that the data used are

secondary, therefore other examinations are needed to determine the cause of anemia, such as peripheral blood picture, iron profile in the blood, and examination of the underlying disease.

In our study, it was found that anemia had a positive correlation with leprosy which indicated that anemia could occur in leprosy patients even before receiving therapy. In addition, the normal MCV, MCH, and MCHC erythrocyte index levels have a positive correlation with leprosy, which describes the morphology of anemia that occurs in leprosy before receiving therapy is normochromic normocytic associated with anemia of chronic disease. Based on this study's results, routine examination of the erythrocyte index should be considered to distinguish the morphology of anemia that occurs in leprosy patients before giving therapy.

CONCLUSION

Leprosy patients had anemia before therapy. The morphology of normochromic normocytic anemia occurs in ± 80% of leprosy patients before therapy is indicated by normal erythrocyte index levels (MCV, MCH, and MCHC) according to anemia of chronic disease. The morphology of hypochromic microcytic anemia occurs in ±20% of leprosy patients before treatment is characterized by low erythrocyte index levels (MCV, MCH, and MCHC), other tests are needed to determine the cause of the hypochromic microcytic. Leprosy patients had anemia before therapy. The morphology of normochromic normocytic anemia occurs in ± 80% of leprosy patients before therapy is indicated by normal erythrocyte index levels (MCV, MCH, and MCHC) according to anemia of chronic disease. The morphology of hypochromic microcytic anemia occurs in ±20% of leprosy patients before treatment is characterized by low erythrocyte index levels (MCV, MCH, and MCHC), other tests are needed to determine the cause of the hypochromic microcytic.

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