RESEARCH PAPER

Association of Serum Zinc Levels with Leprosy Status and Pcr Positivity in an Endemic Island Population of South Sulawesi, Indonesia

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ABSTRACT

Background: Leprosy remains prevalent in developing countries, where zinc influences immune responses and disease progression. Although PCR sensitively detects Mycobacterium leprae, studies comparing zinc levels with PCR results, particularly in island regions such as Selayar, are limited. This study aims to investigate whether zinc levels are associated with the identification of the bacteria-caused leprosy via PCR testing in patients and their contacts.

Method: Using a cross sectional approach, this study was conducted in the Bonerate Islands, Selayar. A total of 75 subjects were included, comprising 20 leprosy patients and 55 contacts, recruited through consecutive sampling. Serum zinc levels were measured using a colorimetric method, while the presence of M. leprae DNA was determined by real time PCR on nasal swab samples.

Results: Serum zinc levels varied significantly between leprosy patients and their contacts ($p = 0.013$), with patients showing lower concentrations. Cut off analysis identified that zinc levels <105.93 µg/dL were significantly associated with leprosy patient status (OR 3.60; 95% CI: 1.15–11.29). PCR testing also demonstrated a meaningful association with patient status (OR = 5.56; $p = 0.019$). No significant association was observed between zinc levels and PCR results ($p > 0.05$).

Conclusion: Low zinc levels are associated with leprosy patient status, reflecting systemic adaptation to chronic infection, but not with PCR detected M. leprae DNA. PCR remains the diagnostic gold standard; zinc levels indicate host response rather than serving as a sole diagnostic marker.

Keywords: Developing countries, Mycobacterium leprae, Immunity, Persistent infection, Zinc

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INTRODUCTION

Leprosy is a long-term, contagious illness caused by the bacterium Mycobacterium leprae. This microorganism primarily targets the skin and the peripheral nervous system. The bacterium tends to proliferate in cooler regions of the body, including the skin and nasal mucosa [1,2].

Despite global control efforts, leprosy remains a public health concern. Over the past two decades, approximately 16 million cases have been reported worldwide, with more than 200,000 new cases annually. Southeast Asia accounts for the majority of cases, and Indonesia remains among the top three countries with the highest burden [3]. In Indonesia, the incidence rate stands at 0.71 cases per 10,000 people, while the rate of new case identification is 6.50 per 100,000 individuals [4].

Persistent transmission in endemic areas suggests the presence of undetected subclinical infections, particularly among household contacts. These individuals may harbor *M. leprae* without clinical manifestations, representing an important reservoir for ongoing transmission [5].

Leprosy incidence is reported to be higher in island regions compared to mainland areas, likely due to limited healthcare access, inadequate preventive measures, and geographic isolation [6,7]. These challenges contribute to delayed diagnosis and continued transmission, especially in remote settings.

Zinc is an essential micronutrient involved in immune regulation, particularly in cell-mediated immunity. Zinc deficiency impairs Th1 responses and reduces cytokine production, including interleukin-2 (IL-2) and interferon-

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gamma (IFN-γ) crucial for controlling intracellular pathogens [8–10]. Previous studies have shown that patients with leprosy tend to have lower serum zinc levels, and adequate zinc status may have a protective role [5,11].

Studies on leprosy in remote islands have been reported in several publications. However, these studies have focused primarily on epidemiological and clinical data [7,12]. Investigations into the molecular factors underlying the high prevalence of leprosy in such remote islands remain rare. Knowledge of these molecular factors could inform the development of more targeted prevention and management strategies for leprosy in these isolated areas, beyond conventional approaches such as improving healthcare access, diagnostic screening, and reducing social stigma. Therefore, this study aims to analyze serum zinc levels in leprosy patients and their contacts to evaluate the relationship between zinc status and the clinical manifestations of the disease, specifically in a single remote island in Indonesia.

METHODS

Study design and subjects

This investigation utilized an analytical observational methodology using a cross-sectional design. The study was conducted in the Bonerate Islands, Kepulauan Selayar Regency, Indonesia (Figure 1). Subjects were recruited using a consecutive sampling method during the study period. Inclusion criteria for the leprosy group were patients newly diagnosed clinically and molecularly with leprosy who had not yet received any leprosy drug therapy. The contact group included individuals with a history of close contact with leprosy patients, either household or neighbouring contacts, for more than three months. Patients with a history of malignancy, autoimmune disease, those classified as malnourished, those who had consumed zinc supplements within the past month, and pregnant patients were excluded from the study. All participants agreed to take part in the research by signing a written informed consent form.

Sample size

The minimum sample size determination in this study was performed using the following formula applicable to unpaired numerical analytical research.

$$n1 = n2 = n3 = 2\,\sigma^2\,\frac{(Z_\alpha + Z_\beta)^2}{(X_1 - X_2)^2}$$

In the calculation, Zα = 2.81 and Zβ = 1.64 were set at the 95% confidence level. According to a previous study [5], the clinically meaningful mean difference ($X_1 - X_2$) was 29.1 (90.0 – 60.9), and the standard deviation (σ) was set at 13.92. Consequently, the minimum sample size calculation yielded 9.06, which was rounded up to 10 samples per group. However, to improve the precision of the study results, we aimed to collect 20 samples per group. Thus, the minimum total sample for this study was 40 samples, with 20 from the leprosy group and 20 from the close contact group.

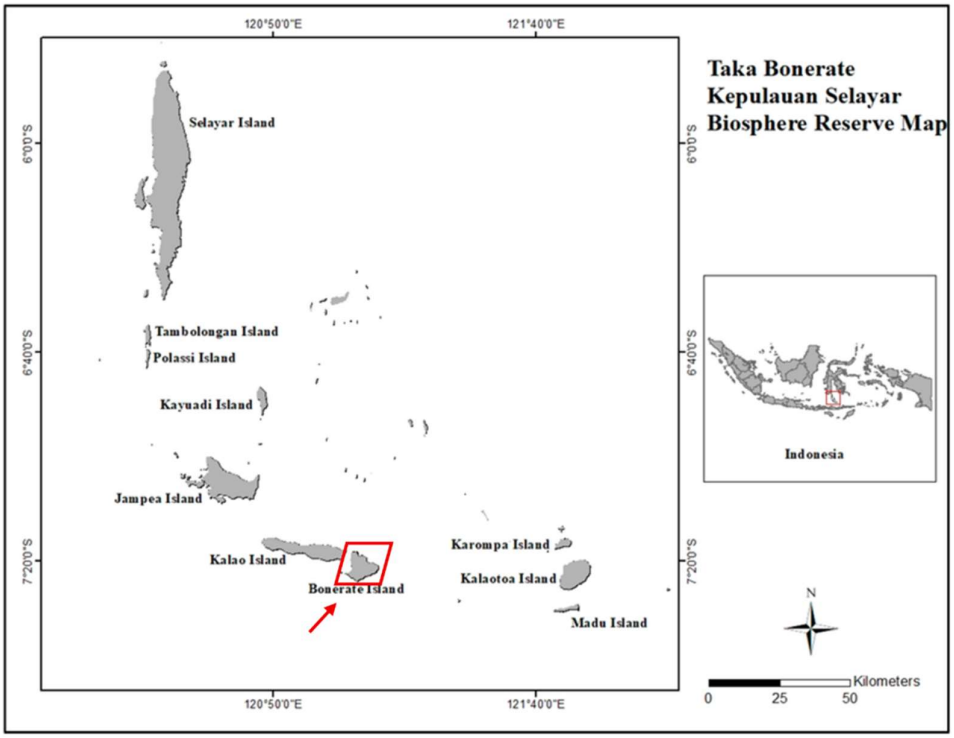

Figure 1: Map of Bonerate Island, Kepulauan Selayar, Indonesia, as the research location (modified from Praptiwi *et al.,* 2021) [13].

Data collection and laboratory examination

Data collection was performed through clinical assessment and laboratory examinations. Blood samples were obtained from all participants to measure the level of serum zinc using standard biochemical laboratory methods. Detection of *M. leprae* DNA was performed using Polymerase Chain Reaction (PCR) analysis. PCR results were interpreted based on cycle threshold (Ct) values, where a Ct value ≤37 was considered positive for *M. leprae*, indicating the presence of bacterial DNA. Additional data collected included demographic characteristics and clinical classification of leprosy (multibacillary or paucibacillary), as well as classification of contacts (household or neighbor). These variables were analyzed to explore their association with zinc levels and PCR results.

Study variables

The primary independent variable in this study was serum zinc level. The main dependent variables were subject status (leprosy patient or contact) and PCR result (positive or negative). Additional variables included leprosy type (multibacillary or paucibacillary) and contact type (household or neighbor), which were used as stratification variables to evaluate subgroup differences further.

Statistical analysis

A comprehensive analysis of all data was conducted utilizing the SPSS software, version 26.0. Appropriate statistical methodologies were applied. Continuous variables were evaluated for normality and subsequently presented as means ± standard deviations, or medians along with their respective ranges (minimum to maximum). Categorical variables, including diagnosis status, zinc status, PCR results, sex, age, body mass index (BMI), and occupation, were presented as frequencies and percentages. The Mann-Whitney U test was employed to compare serum zinc levels between the study groups. Categorical variables underwent analysis using either the chi-square test or Fisher's exact test to determine any potential relationships between the variables. The Receiver Operating Characteristic (ROC) curve analysis was performed to ascertain the optimal threshold for serum zinc levels in relation to leprosy status. Odds ratios (OR) were computed, along with their respective p-values, to assess the strength of these associations. A p-value below 0.05 was considered statistically significant.

Ethical approval

This study was conducted in accordance with ethical principles and received approval from the Health Ethics Committee of our institution on 3 July 2025 (Letter number 466/UN4.6.4.5.31 and protocol number UH25050364). The study complied with the ethical standards set forth by the institutional research ethics board and adhered to the principles outlined in the Declaration of Helsinki. Before data collection, all participants signed a written informed consent form.

RESULTS

Subject characteristics

The study included 75 participants: 20 with leprosy and 55 contacts. Table 1 summarizes their demographic and clinical characteristics. Most were women aged 40-59, with normal nutrition, and primarily engaged in fishing or self-employment. Both groups exhibited a similar distribution of characteristics in terms of sex, age, BMI, and occupation. Overall, the mean zinc level across all samples was 108.14 ± 17.79 µg/dL.

Table 1: Demographic characteristics of study participants

Variables		Leprosy Status		*P-value*
		Contact	Leprosy Patient	
Gender	Male	17 (30.91)	6 (30)	0.940ns#
	Female	38 (69.09)	14 (70)	
Age	<20 years	4 (7.27)	4 (20)	0.454ns##
	20–39 years	16 (29.09)	4 (20)	
	40–59 years	18 (32.73)	6 (30)	
	≥60 years	17 (30.91)	6 (30)	
Body Mass Index	Normal	48 (87.27)	19 (95)	0.755ns##
	Underweight	6 (10.91)	1 (5)	
	Obese 1	1 (1.82)	0 (0)	
Occupancy	Farmer	8 (14.55)	4 (20)	0.095ns##
	Fisherman	12 (21.82)	2 (10)	
	Entrepreneur	13 (23.64)	1 (5)	
	Student	3 (5.45)	4 (20)	
	Housewife	19 (34.55)	9 (45)	
Comparison test: '#' Chi Square Test '##' Fisher's Exact Test				
Significant codes: not significant 'ns'				

Comparison of serum Zinc levels

The comparison of serum zinc levels between leprosy patients and contacts demonstrated a statistically significant difference. Leprosy patients had lower serum zinc levels compared to contacts (p = 0.013). The detailed distribution of zinc levels in both groups is shown in Table 2.

Table 2: Comparison of Zinc value to leprosy status of study participant

Variable	Leprosy Status		*P-value*
	Contact (n=55)	**Leprosy Patient (n=20)**	
Zinc	106.704 (103.597-119.578)	105.164 (103.597-106.704)	0.013*
Comparison test with Mann Whitney Test			
Significant codes: <0.05 '*'			

Cut-off value of serum Zinc levels

The ROC analysis was performed to establish the optimal serum zinc concentration for diagnosing leprosy. The results pinpointed a threshold of 105.93 µg/dL, as shown in Figure 2. In the graph of zinc level versus subject status, the area under the curve (AUC) was 67.5%, indicating a fairly good diagnostic ability to distinguish between leprosy patients and contacts. An AUC value above 0.65 suggests that Zinc level has moderate discriminatory power for subject status. The classification accuracy reached 60%, with a sensitivity of 75% and a specificity of 54.55%. This means that a zinc level below 105.93 µg/dL can identify approximately three-quarters of leprosy patients (fairly sensitive for positive cases). However, there remains a possibility of misclassification among some contacts (moderate specificity). The negative predictive value (NPV) of 85.71% indicates that individuals with zinc levels above the cut-off have a very low probability of being leprosy patients. In contrast, the positive predictive value (PPV) of 37.5% suggests that a low zinc level alone is not sufficiently strong to confirm that a person truly has leprosy. Overall, zinc level may be considered a supportive biomarker for leprosy clinical status, but cannot be used as the sole diagnostic tool.

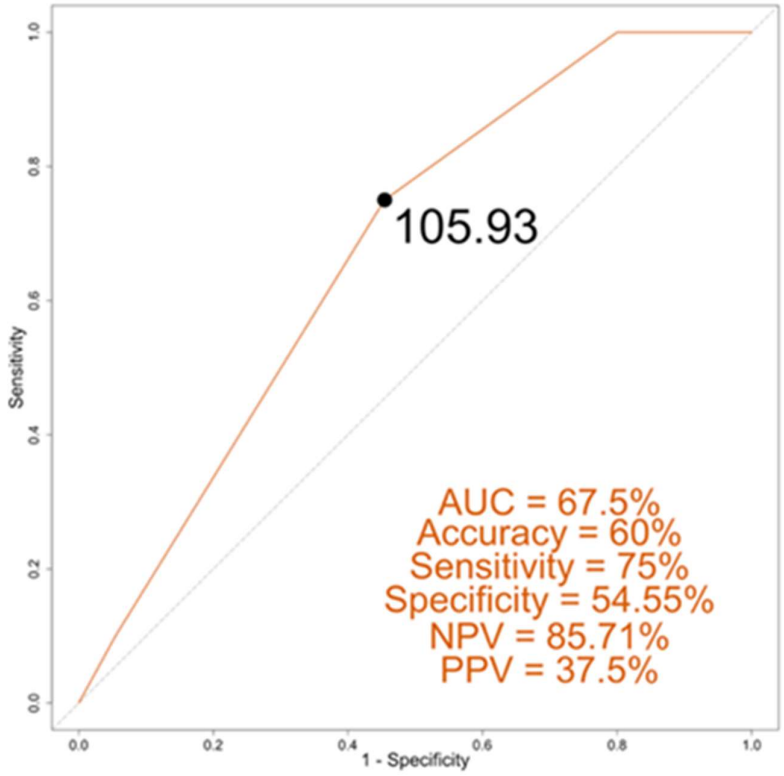

Figure 2: Zinc cut-off value to leprosy status of study participant.

Association of Zinc levels and PCR with leprosy status

Further analysis demonstrated that both low zinc levels and PCR results were significantly associated with leprosy status. Subjects with zinc levels below this threshold had a significantly increased risk of being classified as leprosy patients (OR = 3.60; p = 0.023). In addition, PCR positivity showed a strong association with leprosy status (OR = 5.56; p = 0.019). These findings are summarized in Table 3.

Table 3: Association between Zinc value and PCR results toward leprosy status of study participant.

Variables	Leprosy Status		*P-value*	OR (95% CI)
	Contact (n=55)	**Leprosy Patient**		

			(n=20)		
Zinc	≥105.93µg/dL	30 (54.55)	5 (25)	0.023*	3.60 (1.15-11.29)
	<105.93µg/dL	25 (45.45)	15 (75)		
PCR	Negatif	21 (44.68)	2 (7.14)	0.019*	5.56 (1.17-26.42)
	Positif	34 (72.34)	18 (64.29)		
Comparison test: Chi Square Test					
Significant codes: <0.05 '*'					

Association between Zinc levels and PCR results

The distribution pattern of zinc levels according to PCR results showed that the proportions of high and low zinc levels were relatively balanced across both PCR categories, with only a small percentage difference. The statistical analysis on Table 4 found no significant relationship between serum zinc levels and PCR results (positive or negative). The p-value was above 0.05, showing no statistical significance.

Table 4: Association between Zinc value and PCR results in leprosy patients.

Variable		PCR results		*P-value*	OR (95% CI)
		Negative	Positive		
Zinc	≥105.93µg/dL	10 (43.48)	25 (48.08)	0.713ns	0.83 (0.31-2.23)
	<105.93µg/dL	13 (56.52)	27 (51.92)		
Comparison test: Fisher's Exact Test					
Significant codes: not significant 'ns'					

Subgroup analysis

Subgroup analyses based on leprosy type (multibacillary vs paucibacillary) and contact type (household vs neighbor) showed no statistically significant differences in serum zinc levels or PCR results. These results are presented in Tables 5–6.

Table 5: Association between Zinc value and PCR results toward leprosy contact status.

Variable		Leprosy Contact Status		*P-value*
		Inhouse	Neighbor	
Zinc	≥105.93µg/dL	7 (63.64)	23 (52.27)	0.498ns
	<105.93µg/dL	4 (36.36)	21 (47.73)	
PCR	Negative	4 (36.36)	17 (38.64)	0.890ns
	Positive	7 (63.64)	27 (61.36)	

Comparison test: Chi Square Test. Significant codes: not significant 'ns'

Table 6: Association between Zinc value and PCR results toward morbus hansen subtype.

Variable		Morbus Hansen Subtype		*P-value*
		Multibacillary	Paucibacillary	
Zinc	≥105.93µg/dL	2 (25)	3 (25)	0.999ns
	<105.93µg/dL	6 (75)	9 (75)	
PCR	**Negative**	**2 (25)**	**0 (0)**	**0.147ns**
	Positive	**6 (75)**	**12 (100)**	

Comparison test: Fisher's exact test. Significant codes: not significant 'ns'

DISCUSSION

This study demonstrated that serum zinc levels were significantly lower in leprosy patients compared to contacts. This finding supports the hypothesis that zinc plays an important role in host immunity against Mycobacterium leprae. Zinc is recognized as an essential element for the modulation of cellular immune responses, particularly for the activation of Th1 cells and cytokine production. Specifically, it plays a critical role in the synthesis of cytokines such as the IL-2 and IFN-γ, which are pivotal in the regulation of intracellular pathogen control [8–10].

The lower zinc levels observed in leprosy patients may be explained by the chronic inflammatory state associated with the disease. In cases of persistent infection, zinc is relocated from the bloodstream into tissues as part of the initial immune response, which is driven by pro-inflammatory molecules like IL-6. This process results in decreased circulating zinc levels (hypozincemia), which has been reported in various inflammatory conditions, including leprosy [14].

The ROC analysis in this study identified a cut-off value of 105.93 µg/dL, with lower zinc levels significantly associated with leprosy status. This finding reinforces the potential role of zinc as a biomarker reflecting host susceptibility or immune response rather than a direct indicator of infection. Previous studies have also reported that lower serum zinc levels are associated with leprosy, particularly in multibacillary cases, suggesting that zinc deficiency may contribute to impaired immune control of the infection [15].

PCR examination showed a significant association with leprosy status, confirming its role as a sensitive diagnostic tool for detecting Mycobacterium leprae, including in cases with low bacterial load or subclinical infection. PCR

has been reported to have high sensitivity and specificity, making it useful in both clinical diagnosis and epidemiological surveillance [16].

Interestingly, this study found no significant association between serum zinc levels and PCR results. This suggests that zinc levels are more reflective of the host's immune and inflammatory status rather than the presence or quantity of bacterial DNA. While PCR detects the pathogen directly, zinc reflects the host response to infection, highlighting their complementary roles in understanding leprosy pathogenesis [14].

Subgroup analyses showed no significant differences in zinc levels or PCR results by leprosy type (multibacillary vs paucibacillary) or contact type (household vs neighbor). This may be due to the relatively small sample size or overlapping immunological responses among subgroups. Previous studies have suggested that although multibacillary cases tend to have lower zinc levels, the differences are not always statistically significant in smaller cohorts [17].

From a public health perspective, these findings are particularly relevant in endemic and geographically isolated areas such as island regions, where delayed diagnosis and limited healthcare access may contribute to ongoing transmission. Zinc status may serve as an additional indicator of host vulnerability, especially among contacts who are at risk of developing subclinical infection [6,7].

The cross-sectional design precludes establishing causality. The small sample size restricts generalizability. Serum zinc levels are influenced by nutritional status and systemic inflammation, not fully controlled in this investigation [18]. Further studies should be conducted that include an assessment of the amount and sources of zinc intake in leprosy subjects or contacts in remote islands.

To conclude, serum zinc levels were significantly lower in leprosy patients than in contacts, suggesting a role for zinc in the host immune response against *M. leprae*. A serum zinc cut-off value of 105.93 µg/dL was associated with an increased likelihood of leprosy, indicating that zinc may serve as a useful indicator of host susceptibility. PCR examination showed a significant association with leprosy status and remains a reliable diagnostic tool for detecting *M. leprae*; however, no significant association was found between serum zinc levels and PCR results, implying that zinc reflects the host's immune and inflammatory condition rather than the presence of bacterial DNA. Overall, serum zinc may be considered a complementary parameter for understanding host response in leprosy, while PCR remains essential for diagnostic confirmation. More research is needed to understand zinc's role in leprosy etiology and pathogenesis. Larger cohorts and longitudinal studies are essential to elucidate the mechanisms through which zinc affects disease development and progression.

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Nothing to declare

Conflicts of interest
The authors declare no potential conflict of interest

Authors' contributions
ADP: Study conception and planning; data collection, analysis and interpretation; statistical analysis; preparation and writing of the manuscript; approval of the final version of the manuscript. KD: Study conception and planning; data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. ARNM: Study conception and planning; data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. ANZ: Data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. AAZ: Data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. MNM: Data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. FT: Data analysis and interpretation; critical revision and validating of the manuscript; approval of the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Data availability
Study data is available on request from the corresponding author according to institutional policies.

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