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Original Article

Association Between Vitamin A and Zinc Intake with Inflammatory Markers in Pulmonary Tuberculosis

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Abstract

Background : Indonesia has the second highest burden of tuberculosis (TB) worldwide, with an incidence of 354 per 100,000 population and approximately 969,000 cases reported in 2021. Micronutrients such as vitamin A and zinc play important roles in immune function and may influence inflammatory responses in TB. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are potential markers of systemic inflammation; however, evidence regarding their association with dietary micronutrient intake in pulmonary TB patients remains limited, particularly in Indonesia.
Aims : To examine the association between vitamin A and zinc intake and inflammatory markers in pulmonary TB patients.
Methods : A cross-sectional study was conducted among 133 pulmonary TB patients recruited consecutively from March to April 2024 at Persahabatan Hospital. Vitamin A and zinc intake were assessed using a semi-quantitative food frequency questionnaire (SQ-FFQ), while NLR and PLR values were obtained from medical records. Data normality was tested using the KolmogorovSmirnov test, and correlations were analyzed using Spearman's test. The median vitamin A intake was 105.47 RE/day and zinc intake was 7.38 mg/day, with median NLR and PLR of 2.91 and 202.08, respectively.
Results : No significant correlations were found between vitamin A or zinc intake and NLR or PLR ($p > 0.05$).
Conclusion : In conclusion, vitamin A and zinc intake were not associated with inflammatory markers in pulmonary TB patients, although host-related factors may contribute to the inflammatory response.

Keywords : Inflammation; NLR; TB; vitamin A; zinc

INTRODUCTION

Indonesia has the second-highest burden of tuberculosis (TB) globally, with an incidence of 354 per 100,000 population and approximately 969,000 cases reported in 2021. Despite ongoing national TB control programs, treatment outcomes remain suboptimal, with the treatment success rate still below the national target.[1,2] This highlights the need to explore additional modifiable factors that may influence disease progression and recovery in TB patients.

Malnutrition and TB are closely interrelated in a bidirectional manner. Poor nutritional status can impair immune function, increasing susceptibility to infection and worsening disease severity. Conversely, TB infection can lead to reduced appetite, altered metabolism, and increased energy expenditure, ultimately resulting in nutrient deficiencies. This interaction contributes to delayed recovery, higher risk of complications, and poorer treatment outcomes among affected individuals.

Micronutrients, particularly vitamin A and zinc, play essential roles in maintaining immune competence. Vitamin A is a fat-soluble vitamin involved in epithelial integrity, cellular differentiation, and regulation of both innate and adaptive immune responses. It plays a critical role in maintaining mucosal barriers and modulating the activity of T and B lymphocytes, macrophages, and antibody production. Zinc, on the other hand, is a trace element required for over 300 enzymatic reactions and is crucial for DNA synthesis, cell division, and immune cell function. Zinc deficiency has been associated with impaired phagocytosis, reduced lymphocyte proliferation, and dysregulated inflammatory responses.[3]

In the context of TB, micronutrient deficiencies are highly prevalent and may exacerbate disease progression have demonstrated that patients with active TB often have lower levels of vitamin A and zinc compared to healthy individuals. These deficiencies may impair host defense mechanisms and contribute to prolonged inflammation and delayed bacterial clearance. However, most of the existing evidence has focused on biochemical or serum levels of micronutrients rather than dietary intake, which may provide a more practical and modifiable target for intervention.

Systemic inflammation is a key feature of TB and reflects both disease severity and host immune response. In recent years, simple hematological markers such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have gained attention as indicators of inflammatory status. NLR reflects the balance between neutrophil-mediated innate immunity and lymphocyte-mediated adaptive immunity, while PLR represents the interaction between platelet activation and immune response. Enhancement NLR and PLR values have been associated with increased disease severity, poor prognosis, and treatment response in TB patients.[4,5]

Compared to conventional inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), NLR and PLR are inexpensive, readily available, and can be derived from routine complete blood count examinations. This makes them particularly useful in low-resource settings, where access to advanced laboratory testing may be limited. Furthermore, these markers have been increasingly studied in various infectious and inflammatory diseases, supporting their potential clinical utility.

Despite growing interest in the role of micronutrients and inflammatory markers in TB, there remains a significant gap in the literature. Most previous studies have examined the association between serum micronutrient levels and TB outcomes, while limited research has explored the relationship between dietary micronutrient intake and inflammation. In addition, evidence from Indonesia is still scarce, despite the high burden of TB and the prevalence of nutritional deficiencies in the population.

Furthermore, the inflammatory response in TB is influenced not only by nutritional intake but also by host-related factors such as nutritional status, treatment phase, bacteriological status, and comorbid conditions, including diabetes mellitus. These factors may act as confounders and contribute to variability in inflammatory markers, yet they have not been comprehensively evaluated in relation to dietary intake in previous studies.

Therefore, this study aimed to examine the association between vitamin A and zinc intake with inflammatory markers, specifically NLR and PLR, among pulmonary TB patients at Persahabatan Hospital. This study also explored the potential influence of selected host-related factors on inflammatory responses. Understanding these relationships may provide insight into the role of nutrition in TB management and support the development of integrated strategies to improve patient outcomes. This study is among the first in Indonesia to examine dietary micronutrient intake in relation to hematological inflammatory markers in pulmonary TB patients.

METHODS

This study employed an observational analytical design with a cross-sectional approach conducted at Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia, between March and April 2024.

A consecutive sampling recruited among 133 subjects.

Inclusion criteria were adults aged ≥18 years with a confirmed diagnosis of pulmonary TB established by the attending physician based on clinical, radiological,

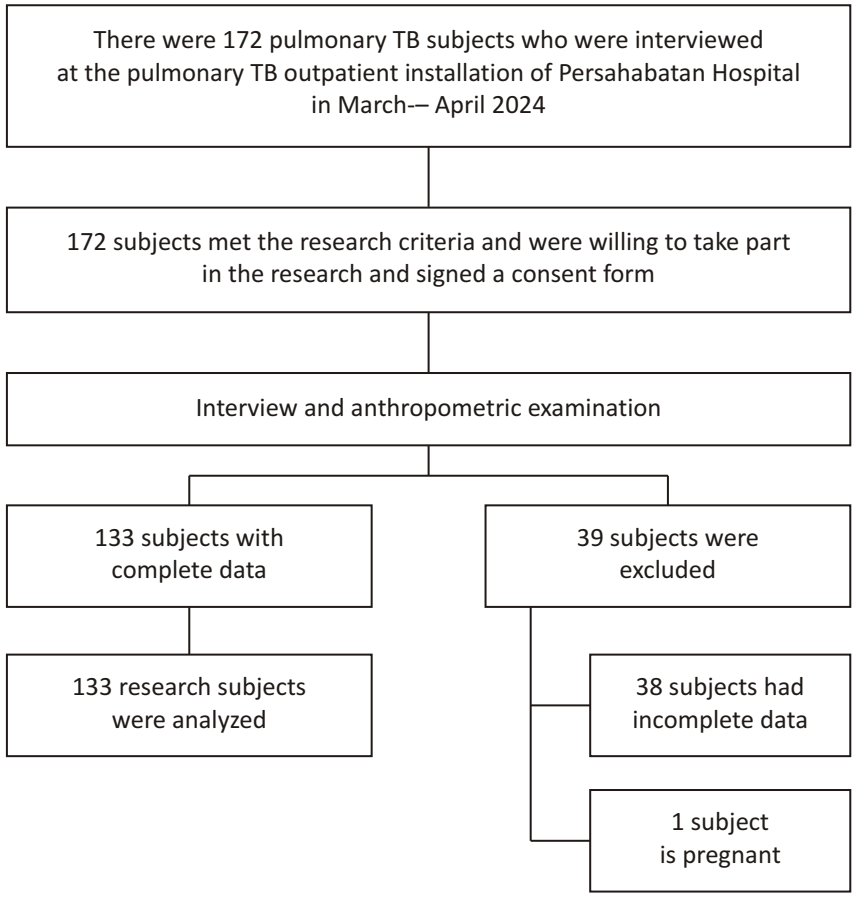

Figure 1. Research sample selection flow

and/or microbiological findings, who agreed to participate and provided written informed consent. Exclusion criteria included incomplete laboratory data (neutrophil, lymphocyte, or platelet counts), laboratory results obtained more than one month prior to data collection, pregnancy, breastfeeding, and suspected or confirmed HIV infection based on medical history or laboratory findings.

Data collection was performed through structured interviews, anthropometric measurements, and medical record review. Trained researchers conducted face-to-face interviews using standardized questionnaires to obtain information on demographic characteristics, educational level, income, smoking history, comorbidities, and medication use.

Dietary intake over the previous month was assessed using a semi-quantitative food frequency questionnaire (SQ-FFQ) consisting of commonly consumed Indonesian food items. The SQ-FFQ instrument had been previously validated in Indonesian populations. Portion sizes were estimated using a standardized food photograph atlas published by the Ministry of Health. Reported food intake was converted into grams using household measurement standards.

Nutrient intake was analyzed using NutriSurvey 2007 software based on the Indonesian Food Composition Table. Vitamin A intake was expressed as retinol equivalents (RE) per day, while zinc intake was expressed in milligrams per day.

The adequacy of micronutrient intake was determined based on the 2019 Indonesian Recommended Dietary Allowance (RDA). Vitamin A intake was categorized as adequate if ≥600 RE/day and inadequate if <600 RE/day. Zinc intake was classified as adequate if ≥8 mg/day and inadequate if <8 mg/day. The classification of micronutrient adequacy was also supported by previous studies in Indonesian populations.[26,27]

Anthropometric measurements included body weight and height, measured twice using a calibrated digital scale (SECA 876) and a ShorrBoard stadiometer with an accuracy of 0.1 cm. The average of the two measurements was used for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and classified according to the WHO Asia-Pacific criteria.

Inflammatory markers were obtained from routine complete blood count results recorded in patients' medical records. The neutrophil-to-lymphocyte ratio

(NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, while the platelet-to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the absolute lymphocyte count.

Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the KolmogorovSmirnov test. Continuous variables were presented as mean ± standard deviation for normally distributed data or median (minimum–maximum) for non-normally distributed data, while categorical variables were presented as frequencies and percentages.

Correlation analysis between vitamin A and zinc intake and inflammatory markers (NLR and PLR) was conducted using Pearson correlation for normally distributed data or Spearman's rank correlation test for non-parametric data. A p-value <0.05 was considered statistically significant.

This study was approved by the Research Ethics Committee of Persahabatan Hospital (No. 0034/KEPK-RSUPP/02/2024). All participants provided written informed consent prior to enrollment. Confidentiality of participants' data was maintained throughout the study, and all procedures were conducted in accordance with ethical standards for human research.

RESULTS

A total of 133 pulmonary TB (TB) patients were included in this study. The age of participants ranged from 19 to 74 years, with a median age of 39 years, indicating a predominance of individuals in the productive age group. Male participants slightly outnumbered females, accounting for 51.9% of the sample. In terms of educational background, most subjects had a moderate level of education (57.1%), while 26.3% had low education and 16.5% had higher education.

The largest proportion of participants had normal body mass index (42.1%), followed by underweight individuals (36.8%). A smaller proportion were classified as overweight (8.3%) and obese (12.8% combined for obese I and II). These findings indicate that although a considerable number of patients had normal nutritional status, undernutrition remained highly prevalent among TB patients in this cohort.

Most participants (83.5%) had an income below the regional minimum wage, reflecting a predominantly low socioeconomic background. Regarding treatment characteristics, 46.6% of subjects were in the intensive phase of anti-TB therapy, 26.3% were in the continuation phase, and 27.1% were classified as having drug-resistant TB. Bacteriological examination showed that 51.9% of patients were positive, while 48.1% were negative at the time of data collection.

The majority of subjects (59.4%) reported no comorbidities. Among those with comorbid conditions, diabetes mellitus was the most common (15.8%), followed by cardiovascular disease (6.0%), while smaller proportions reported cancer or chronic respiratory diseases. Smoking history revealed that 57.1% of participants had never smoked, whereas 20.3% were light smokers and 16.5% were moderate to heavy smokers.

In terms of medication use, 67.7% of participants reported no additional drug consumption aside from anti-TB therapy. Among those who used concomitant medications, the most commonly reported were antihypertensive drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and gastrointestinal medications such as antacids or proton pump inhibitors.

Dietary assessment revealed that the majority of participants had inadequate micronutrient intake. A total of 94.7% of subjects had vitamin A intake below the recommended dietary allowance, while 56.4% had inadequate zinc intake. The median vitamin A intake was 105.47 RE/day (range 4.26–1854.90), and the median zinc

TABLE 1
Characteristics of the Study Participants (n= 133)

Variables	Proportion n (%)	Median (min–max)
Age		39 (19–74)
Gender		
Male	69 (51.9)	
Female	64 (48.1)	
Level of education		
Low	35 (26.3)	
Medium	76 (57.1)	
High	22 (16.5)	

TABLE 1. *Continued.*

Variables	Proportion n (%)	Median (min–max)
Nutritional status		
Underweight	49 (36.8)	
Normal	56 (42.1)	
Overweight	11 (8.3)	
Obese I	12 (9.0)	
Obese II	5 (3.8)	
Income		
Below minimum wage	111 (83.5)	
Above minimum wage	22 (16.5)	
Treatment Phase		
Intensive Phase	62 (46.6)	
Continuation Phase	35 (26.3)	
Drug Resistant	36 (27.1)	
Bacteriological Status		
Positive	69 (51.9)	
Negative	64 (48.1)	
Comorbid		
None	79 (59.4)	
Cardiovascular disease	8 (6.0)	
Cancer	2 (1.5)	
Chronic respiratory disease	2 (1.5)	
Diabetes	21 (15.8)	
Other	20 (15.0)	
Smoking Habit		
Never	76 (57.1)	
Mild	27 (20.3)	
Moderate	22 (16.5)	
Heavy	8 (6.0)	
Drug Consumption		
None	90 (67.7)	
Antacids, PPI, H2 receptor blockers	4 (3.0)	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	9 (6.8)	
Mineral Supplements (Fe, Ca, Cu)	–	
Antihypertensives (ACE inhibitors, loop diuretics, thiazides)	9 (6.8)	
Antibiotics (ciprofloxacin, tetracycline)	1 (0.8)	
Other	29 (21.8)	

TABLE 1. *Continued.*

Variables	Proportion n (%)	Median (min–max)
Vitamin A Intake		
Inadequate	126 (94.7)	
Adequate	7 (5.3)	
Zinc Intake		
Inadequate	75 (56.4)	
Adequate	58 (43.6)	

TABLE 2
Distribution of Intake of Vitamin A, Zinc, and Inflammatory markers

Variables	Median (min–max)
Vitamin A Intake (RE)	105.47 (4.26–1854.90)
Zinc Intake (mg)	7.38 (1.74–40.47)
Inflammatory markers	
NLR	2.91 (0.75–26.26)
PLR	202.08 (9.82–1516.24)

TABLE 3
Correlation between Vitamin A and Zinc Intake and Inflammatory markers

Variables	Inflammatory markers			
	NLR		PLR	
	r	*p* value	r	*p* value
Vitamin A Intake	0.077	0.379[S]	0.059	0.497[S]
Zinc Intake	0.104	0.234[S]	0.130	0.137[S]

*[S] Spearman test

intake was 7.38 mg/day (range 1.74–40.47). These findings indicate a substantial gap between actual intake and recommended levels, particularly for vitamin A.

Regarding inflammatory markers, the median neutrophil-to-lymphocyte ratio (NLR) was 2.91 (range 0.75–26.26), while the median platelet-to-lymphocyte ratio (PLR) was 202.08 (range 9.82–1516.24). These values reflect a wide variability in systemic inflammatory response among TB patients.

Correlation analysis using Spearman's test demonstrated that there was no statistically significant association between vitamin A intake and NLR (r = 0.077; p = 0.379) or PLR (r = 0.059; p = 0.497). Similarly, zinc intake was not significantly correlated with NLR (r = 0.104; p = 0.234) or PLR (r = 0.130; p = 0.137). These results indicate that dietary intake of vitamin A and zinc did not show a measurable relationship with inflammatory markers in this study population.

Further exploratory analyses were conducted to assess the potential influence of host-related factors on inflammatory markers. Patients with underweight nutritional status tended to have higher median NLR and PLR values compared to those with normal or higher BMI, suggesting a possible association between poor nutritional status and increased inflammatory response. Additionally, subjects in the intensive phase of TB treatment showed relatively higher NLR values compared to those in the continuation phase, reflecting

more active inflammation during early treatment.

Patients with comorbid diabetes mellitus also demonstrated a tendency toward higher PLR values compared to those without comorbidities. Similarly, individuals with drug-resistant TB appeared to have elevated inflammatory markers compared to drug-sensitive cases. However, these differences did not reach statistical significance in this study.

Overall, while micronutrient intake––specifically vitamin A and zinc––was largely inadequate among participants, no direct correlation was found with inflammatory markers (NLR and PLR). Instead, descriptive trends suggest that inflammatory responses in pulmonary TB patients may be influenced by a combination of nutritional status, treatment phase, and comorbid conditions rather than micronutrient intake alone.

DISCUSSION

The findings demonstrated that the majority of participants had inadequate intake of vitamin A and zinc; however, no statistically significant association was observed between micronutrient intake and inflammatory markers. These results highlight the complexity of the relationship between nutrition and immune response in TB. This finding suggests that dietary intake alone may not reflect inflammatory status in TB patients.

The high prevalence of inadequate vitamin A intake (94.7%) observed in this study is consistent with previous findings in TB populations, where micronutrient deficiencies are common due to both inadequate dietary intake and disease-related metabolic alterations.[6,28] Vitamin A plays a crucial role in maintaining epithelial integrity and modulating immune responses, particularly through its involvement in T- and B-lymphocyte differentiation and antibody production.[3] Despite its well-established immunological role, the lack of association between dietary vitamin A intake and inflammatory markers in this study suggests that intake alone may not directly reflect functional immune status in TB patients.

Similarly, more than half of the participants (56.4%) had inadequate zinc intake, which is in line with previous studies conducted in TB populations.[6,12] Zinc is essential for numerous biological processes, including DNA synthesis, cell division, and immune function. Previous interventional studies on zinc supplementation have also reported mixed effects on inflammatory outcomes.[3,23] It also plays a key role in maintaining immune integrity by supporting macrophage activity, neutrophil function, and lymphocyte proliferation. Micronutrients, including vitamin D, have also been shown to influence immune responses in TB.[31] The absence of a significant relationship between zinc intake and NLR or PLR in this study may be explained by the complex regulation of zinc metabolism during infection.

One possible explanation for the lack of significant associations is the effect of the acute-phase response during TB infection. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) can influence the metabolism and redistribution of micronutrients. During inflammation, both vitamin A and zinc are redistributed from circulation to tissues, resulting in decreased plasma concentrations regardless of intake.[28,29] This phenomenon may obscure the relationship between dietary intake and circulating biomarkers, including hematological inflammatory indices such as NLR and PLR.

Another important consideration is that dietary intake assessed using SQ-FFQ reflects habitual consumption rather than actual bioavailability or absorption. Factors such as dietary composition, presence of inhibitors (e.g., phytates), and individual differences in metabolism can significantly affect nutrient utilization.[13,14] For instance, zinc absorption is inhibited by phytate-rich foods, while vitamin A absorption depends on adequate dietary fat intake.[14,15] Therefore, measured intake may not accurately represent the effective nutrient status influencing immune responses.

The median NLR value of 2.91 observed in this study is consistent with previous reports indicating elevated NLR levels in TB patients.[22,37] NLR reflects the balance between innate and adaptive immune responses, where increased neutrophils indicate acute inflammation and decreased lymphocytes reflect immune redistribution.[3] Although NLR has been proposed as a useful marker for disease severity and treatment response, its relationship with nutritional factors appears to be indirect and influenced by multiple confounding variables.

Similarly, the median PLR value of 202.08 suggests an elevated inflammatory state among participants. Platelets are increasingly recognized as active participants in immune and inflammatory processes, interacting with leukocytes and contributing to cytokine release.[11] Elevated PLR has been associated with disease severity in TB and other chronic inflammatory conditions.[11] However, as with NLR, PLR may be more reflective of overall disease activity rather than specific nutritional intake.

Although no statistically significant correlations were identified, exploratory analyses in this study suggested that host-related factors may play a more prominent role in influencing inflammatory markers. Patients with underweight status tended to have higher NLR and PLR values, supporting previous evidence that malnutrition exacerbates systemic inflammation and impairs immune regulation.[1] Malnutrition can lead to reduced immune cell production and altered cytokine responses, thereby intensifying inflammatory

processes.[26,27]

Treatment phase also appeared to influence inflammatory markers. Patients in the intensive phase of anti-TB therapy demonstrated higher NLR values compared to those in the continuation phase. This finding is supported by previous studies showing that inflammatory markers tend to decrease following treatment initiation.

Comorbid diabetes mellitus was another factor associated with higher PLR values in this study. Diabetes is known to impair immune function and promote chronic inflammation, increasing susceptibility to TB and worsening outcomes.[21] Additionally, hyperglycemia can enhance platelet activation and inflammatory responses, potentially influencing PLR values.[2]

The findings of this study differ from some previous research that reported significant associations between serum micronutrient levels and TB outcomes. For example, studies have shown that low serum vitamin A and zinc levels are associated with worse clinical outcomes in TB patients.[12,30,31] This discrepancy may be attributed to differences in measurement methods, as this study assessed dietary intake rather than biochemical levels.

This study provides important insights into the nutritional and inflammatory profiles of TB patients in Indonesia. By focusing on dietary intake rather than biochemical measurements, it offers a practical perspective relevant for clinical and public health interventions. However, the findings also underscore the limitations of using dietary intake alone to assess the relationship between nutrition and immune function in infectious diseases.

Several limitations should be considered. The cross-sectional design limits causal interpretation, and dietary data collection using SQ-FFQ may introduce recall bias. Additionally, the absence of biochemical measurements limits the ability to fully assess micronutrient status.[13] Despite these limitations, this study contributes valuable baseline data for future research.

Future studies should consider longitudinal designs and incorporate both dietary and biochemical assessments to better understand the dynamic relationship between nutrition and inflammation in TB. Similar findings have been reported in South Asian populations, where nutritional status was associated with inflammatory markers.[32,33] Furthermore, larger sample sizes and inclusion of additional biomarkers may help clarify the observed associations.

From a clinical perspective, the findings emphasize the importance of integrating nutritional assessment into TB management. Although no direct association was found between micronutrient intake and inflammatory markers, ensuring adequate nutrient intake remains essential for supporting immune function and recovery.[32] These findings emphasize that nutritional interventions in TB should not rely solely on intake assessment but consider comprehensive host and disease-related factors.

CONCLUSION

This study found that there was no statistically significant association between dietary intake of vitamin A and zinc and inflammatory markers, as measured by neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), among pulmonary TB patients at Persahabatan Hospital. Despite the absence of a direct correlation, the findings revealed that the majority of patients had inadequate intake of these essential micronutrients, highlighting a substantial nutritional gap in this population.

The results suggest that inflammatory responses in TB are not solely influenced by micronutrient intake but are likely determined by a complex interplay of multiple host-related factors. Exploratory analyses indicated that nutritional status, phase of anti-TB treatment, drug resistance status, and comorbid conditions such as diabetes mellitus may contribute to variations in inflammatory markers. Although these associations did not reach statistical significance, they demonstrate consistent trends that align with biological plausibility and existing literature.

These findings underscore the importance of adopting a more comprehensive approach in understanding the relationship between nutrition and immune response in TB. While dietary intake alone may not directly correlate with hematological inflammatory markers, adequate micronutrient consumption remains essential for maintaining immune function, supporting recovery, and improving overall clinical outcomes. Therefore, nutritional assessment should be considered an integral component of routine TB management.

From a clinical and public health perspective, integrating nutritional evaluation and counseling into TB care may provide a low-cost and feasible strategy to support patient recovery, particularly in resource-limited settings. In addition, simple inflammatory markers such as NLR and PLR may still serve as useful adjunct tools for monitoring disease progression when interpreted alongside clinical and nutritional factors.

Future research should focus on longitudinal study designs to capture dynamic changes in both micronutrient status and inflammatory responses during treatment. The inclusion of biochemical measurements, such as serum vitamin A and zinc levels, alongside dietary assessment, would provide a more comprehensive understanding of nutrientimmune interactions. Larger, multicenter studies are also needed to confirm these findings and to further explore the combined effects of nutritional and clinical variables on

TB outcomes.

In conclusion, although no significant association was observed between vitamin A and zinc intake and inflammatory markers in this study, the high prevalence of inadequate intake and the influence of host-related factors highlight the need for integrated nutritional and clinical management strategies in TB care.

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CONFLICT OF INTEREST

The authors declared there is no conflict of interest.

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