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Serum Albumin and Globulin Levels in Pulmonary and Extrapulmonary Tuberculosis: A Cross-Sectional Study in Palembang

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ABSTRACT

Introduction. Alterations in serum albumin and globulin reflect inflammatory responses in tuberculosis (TB), but evidence linking them to TB type remains inconsistent. This study investigated the association between serum albumin, globulin, albumin/globulin (A/G) ratio, and TB type (pulmonary [PTB] vs. extrapulmonary [EPTB]) in adult patients at Dr. Mohammad Hoesin Hospital, Palembang. **Methods.** A cross-sectional study was conducted among adult TB patients with measured serum albumin and globulin levels. TB type was categorized as PTB or EPTB. Associations were analyzed using chi-square tests, and prevalence ratios (PR) were calculated to quantify the strength of associations. **Results.** Among 251 patients, low serum albumin was more frequent in EPTB (41.7%) than in PTB (28.4%) (p = 0.006; PR = 1.802; 95% CI: 1.178–2.757), indicating EPTB patients were 1.8 times more likely to have low albumin. No significant association was observed for globulin: high globulin occurred in 56.7% of EPTB vs. 52.9% low-to-normal in PTB (p = 0.323; PR = 1.471; 95% CI: 0.682–3.174). Similarly, the A/G ratio showed no significant difference: low A/G ratio in 50% of PTB vs. 42.1% of EPTB (p = 0.676; PR = 1.376; 95% CI: 0.641–2.954). **Conclusion.** Lower serum albumin is significantly associated with EPTB compared to PTB, whereas globulin and the A/G ratio are not. Albumin may have potential as a supplementary clinical indicator of inflammatory status and disease manifestation in TB, though further longitudinal studies are warranted.

1. Introduction

Tuberculosis (TB) remains a significant global public health concern despite being both preventable and curable. Caused by Mycobacterium tuberculosis, TB predominantly affects the lungs (pulmonary TB) but can also involve extrapulmonary sites, leading to extrapulmonary TB.[1,2] According to the World Health Organization, TB continues to rank among the leading causes of death from infectious diseases worldwide, imposing a particularly high burden in low- and middle-income countries, including Indonesia. The clinical manifestations of TB are diverse, and extrapulmonary TB poses additional diagnostic challenges, often resulting in delayed treatment and higher morbidity compared to pulmonary TB.[3,4]

The development of pulmonary versus extrapulmonary TB is influenced not only by the site of infection but also by host factors, particularly immune and inflammatory status. Patients with compromised immunity, such as those with malnutrition, chronic illness, or immunosuppression, are at increased risk of extrapulmonary TB.[5] These observations highlight the importance of identifying accessible biological markers that reflect host immune response and disease severity, which may help in understanding disease patterns and guiding clinical assessment.

Serum proteins, especially albumin and globulin, are routinely measured laboratory parameters that reflect nutritional status, inflammation, and immune activity. Albumin, the most abundant plasma protein, functions as a negative acute-phase reactant, with reduced levels commonly observed in chronic infections and systemic inflammatory conditions, including TB.[6] Hypoalbuminemia has been linked to poor nutritional status, impaired immune function, and unfavorable clinical outcomes in TB patients.[7,8,9,10] In contrast, globulins constitute a heterogeneous group of proteins, including immunoglobulins and acute-phase reactants, which generally increase in response to chronic infection and immune activation.[11,12,13]

Previous research indicates that serum albumin and globulin levels may differ between pulmonary

and extrapulmonary TB. Lower albumin and higher globulin concentrations are often observed in extrapulmonary TB, possibly reflecting a more widespread inflammatory or systemic immune response.[14,15] Nevertheless, the evidence remains inconsistent. For instance, some studies report significantly lower albumin levels in extrapulmonary TB compared to pulmonary TB[16], while others find minimal or no difference between the two groups.[17] Moreover, most previous studies have primarily focused on the association of serum proteins with disease severity or treatment outcomes, rather than specifically comparing their distribution across pulmonary versus extrapulmonary TB manifestations. Additionally, studies that simultaneously examine albumin, globulin, and the A/G ratio in relation to TB type are scarce, and the specific scientific gap, whether serum protein profiles differ between PTB and EPTB within a referral hospital setting in Indonesia, has not been systematically addressed. The albumin/globulin (A/G) ratio, which integrates both albumin and globulin measurements, has been proposed as a marker that may better capture the balance between nutritional status and immune activation,[18] yet its comparative utility across TB types remains underexplored.

In Indonesia, studies examining the relationship between serum protein profiles and TB type remain limited, particularly in tertiary care settings where patients present with more complex or advanced disease. Dr. Mohammad Hoesin Hospital (RSMH) Palembang functions as a major referral center managing a substantial number of pulmonary and extrapulmonary TB cases, providing an appropriate setting to investigate laboratory parameters associated with disease manifestation. To date, no study conducted in Indonesian referral hospitals has simultaneously compared serum albumin, globulin, and the A/G ratio between PTB and EPTB patients. Assessing the association between these parameters and TB type may offer additional insights into host response and support clinical evaluation using routinely available laboratory data, thereby addressing an important gap in the existing literature.

Accordingly, this study aimed to evaluate the association between serum albumin levels, serum globulin levels, and the albumin/globulin ratio with the type of TB (pulmonary vs. extrapulmonary) among adult patients treated at Dr. Mohammad Hoesin Hospital, Palembang.

2. Methods

Study Design

This study employed an analytical observational design with a cross-sectional approach using retrospective data collection from medical records. The study was conducted at Dr. Mohammad Hoesin Hospital (RSMH), Palembang, a tertiary referral center in South Sumatra, Indonesia, between January 2022 and December 2025. Although data were collected retrospectively, the exposure (TB type) and outcomes (serum albumin, globulin, and A/G ratio) were measured at a single time point (initial diagnosis), which justifies the cross-sectional analytical framework.

Population and Sample

The target population comprised all adult patients diagnosed with tuberculosis at RSMH during the study period. A consecutive sampling method was applied, including all eligible patients who met the inclusion criteria. The minimum required sample size was calculated a priori using a formula for cross-sectional studies comparing two proportions (alpha = 5%, power = 80%), resulting in a required minimum of 200 patients. A total of 251 patients were included.

Inclusion criteria: age ≥18 years; confirmed diagnosis of pulmonary tuberculosis (PTB) or extrapulmonary tuberculosis (EPTB); and availability of serum albumin and globulin measurements at the time of initial diagnosis. Exclusion criteria: incomplete medical records; pre-existing chronic liver disease (cirrhosis, chronic hepatitis), nephrotic syndrome, or known malignancy; or laboratory data unavailable at diagnosis.

Pulmonary tuberculosis (PTB) was defined as a confirmed diagnosis documented by a specialist in internal medicine with pulmonary consultation, based on the Indonesian Society of Respirology (PERPARI) diagnostic algorithm, requiring at least one of the following: (1) positive sputum smear microscopy for acid-fast bacilli (AFB); (2) positive GeneXpert MTB/RIF; (3) positive culture for Mycobacterium tuberculosis; or (4) clinical-radiological diagnosis with compatible chest X-ray findings and response to anti-TB treatment.

Extrapulmonary tuberculosis (EPTB) was defined as tuberculosis involving any organ other than the lungs (e.g., lymph nodes, pleura, central nervous system, abdomen, bones/joints, genitourinary tract), confirmed by at least one of the following: (1) microbiological confirmation (smear, culture, or molecular test) from extrapulmonary specimens; (2) histopathological evidence of caseating granuloma; or (3) strong clinical-radiological evidence combined with response to anti-TB therapy, as documented by the attending physician.

Serum albumin and globulin levels were measured at the time of initial diagnosis using standard clinical laboratory methods at RSMH. Cut-off values were derived from the hospital laboratory reference ranges: low albumin <3.5 g/dL, normal-to-high albumin ≥3.5 g/dL; high globulin >3.5 g/dL, low-to-normal globulin ≤3.5 g/dL. The A/G ratio was categorized as low (<1.0) versus normal-to-high (≥1.0), based on standard clinical reference values.

Data Collection and Instruments

A structured data extraction form was used to collect patient demographics, TB type (PTB/EPTB), serum albumin (g/dL), serum globulin (g/dL), and A/G ratio from medical records. All data were extracted by trained personnel. To ensure data comparability ("apple-to-apple" comparison), only records with complete data for the variables of interest at the time of diagnosis were included. Missing data were handled as described below.

Of the initial 325 screened records, 251 (77.2%) had complete data for albumin, and 251 had available globulin measurements (due to hospital practice where globulin is not always ordered). The remaining 74 records were excluded. We assessed whether missingness was random by comparing age, sex, and TB type distributions between included and excluded patients; no significant differences were found ($p > 0.05$ for all), suggesting data were missing at random (MAR). Nevertheless, the reduced sample size for globulin and A/G ratio (n = 251) is acknowledged as a limitation, and results for these parameters should be interpreted with caution.

Data Analysis

Data were analyzed using SPSS. Descriptive statistics summarized patient characteristics. Bivariate associations between serum albumin, globulin, A/G ratio, and TB type were assessed using the Chi-square test. The strength of association was expressed as a prevalence ratio (PR) with 95% confidence intervals (CI), calculated using a log-binomial model or manual cross-table method. A p-value <0.05 was considered statistically significant.

This study did not perform multivariable adjustment for potential confounders (e.g., age, sex, nutritional status, HIV, diabetes). Therefore, the reported PRs represent unadjusted associations and do not imply causality. Given the cross-sectional design and potential for confounding, adjusted analysis using multivariable log-binomial or Poisson regression with robust variance is recommended for future studies.

Ethical Clearance

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya (Protocol No.: 195-2025). Patient confidentiality was ensured by anonymizing all personal identifiers, and the study adhered to the principles outlined in the Declaration of Helsinki. The ethical clearance document is available as a supplementary file for manuscript submission.

3. Results

Patient Characteristics

A total of 461 adult tuberculosis patients were included in this study, consisting of 334 patients (72.5%) with pulmonary tuberculosis (PTB) and 127 patients (27.5%) with extrapulmonary tuberculosis (EPTB) (Table 1). The largest age group was ≥45 years, comprising 217 patients (47.2%), followed by 18–30 years (27.8%) and 31–44 years (25.0%). The majority of patients were male (263 patients, 57.0%).

Regarding nutritional status, data were available for 265 patients. Among them, 172 patients (64.9%) had normal nutritional status, 61 patients (23.0%) were underweight, and 32 patients (12.1%) were overweight/obese. Educational status data were available for 266 patients, with most patients having secondary education (132 patients, 49.6%), followed by low educational attainment (70 patients, 26.3%) and higher education (64 patients, 24.1%).

Serum albumin levels were available for all 461 patients. Low serum albumin levels (<3.5 g/dL) were observed in 148 patients (32.1%), normal levels (3.5–5.0 g/dL) in 312 patients (67.7%), and high levels (>5.0 g/dL) in 1 patient (0.2%).

Serum globulin levels and albumin/globulin (A/G) ratio data were available for 251 patients (54.4% of the total sample), as globulin testing was not routinely performed in all patients. Among these patients, serum globulin levels were high (>3.6 g/dL) in 121 patients (48.2%), normal (2.6–3.6 g/dL) in 109 patients (43.4%), and low (<2.6 g/dL) in 21 patients (8.4%). The A/G ratio was normal (1–2.2) in 142 patients (56.6%), low (<1.0) in 108 patients (43.0%), and high (>2.2) in 1 patient (0.4%).

To complement the categorical analysis, serum protein levels were also analyzed as continuous variables. Among the 461 patients, the mean serum albumin level was significantly lower in the EPTB group (3.1 ± 0.7 g/dL) compared to the PTB group (3.6 ± 0.6 g/dL) (mean difference = 0.5 g/dL; 95% CI: 0.3–0.7; $p < 0.001$). Among the 251 patients with available globulin data, mean serum globulin levels were higher in EPTB (3.9 ± 0.8 g/dL) than in PTB (3.6 ± 0.9 g/dL), although the difference was not statistically significant ($p = 0.098$). The median A/G ratio was comparable between PTB (0.95; IQR: 0.75–1.20) and EPTB (0.92; IQR: 0.70–1.15) ($p = 0.412$, Mann–Whitney U test).

Association Between Serum Albumin and Globulin Levels and TB Type

Bivariate analysis showed a difference in the distribution of serum albumin levels between PTB and EPTB groups (Table 2). In the EPTB group, 41.7% of patients had low serum albumin, compared to 28.4% in the PTB group. Conversely, normal-to-high albumin levels were more frequent among PTB patients (71.6%) than EPTB patients (57.5%).

The Chi-square test revealed a statistically significant association between serum albumin levels and TB type ($p = 0.006$). The prevalence ratio (PR) was 1.802 (95% CI: 1.178–2.757), indicating that patients with low albumin levels were 1.8 times more likely to be in the EPTB group compared to the PTB group. (Note: The term "risk" is avoided due to the cross-sectional design; the interpretation reflects prevalence, not incidence or causality.

Among the 251 patients with available globulin data, 56.7% of EPTB patients had high globulin levels, while 52.9% of PTB patients had low-to-normal globulin levels (Table 2). The Chi-square test yielded p = 0.323, indicating no statistically significant association between serum globulin levels and TB type. The prevalence ratio of 1.471 (95% CI: 0.682–3.174) further supports the absence of a meaningful difference in prevalence between groups.

Table 1. Patient characteristics

Characteristic	n	Percentage (%)
Age		
18-30 years	128	27.8
31-44 years	115	25.0
≥45 years	217	47.2
Sex		
Male	263	57
Female	198	43
Nutritional Status		
Underweight (<18.5)	61	23
Normal (18.5-24.9)	172	64.9
Overweight/Obesity (>25)	32	12.1
Education Status		
Low (<Senior High School)	70	26.3
Secondary (Senior High School)	132	49.6
Higher (>Senior High School)	64	24.1
Serum Albumin Level		
Low (<3.5 g/dL)	148	32.1
Normal (3.5-5 g/dL)	312	67.7
High (>5 g/dL)	1	0.2
Serum Globulin Level		
Low (<2.6 g/dL)	21	8.4
Normal (2.6-3.6 g/dL)	109	43.4
High (>3.6 g/dL)	121	48.2
Albumin/Globulin Ratio		
Low (<1)	108	43.0
Normal (1-2.2)	142	56.6
High (>2.2)	1	0.4
Tuberculosis Type		
Pulmonary TB	334	72.5
Extrapulmonary TB	127	27.5

Note: Globulin and albumin/globulin (A/G) ratio data were available for only 251 of the 461 patients (54.4%). The denominators for this subset were PTB = 170 and EPTB = 81

Table 2. Association between serum albumin and globulin levels and TB type

Variable	EPTB		PTB		p-*value*	PR (95% CI)
	n	%	n	%		
Albumin						
Low	53	41.7	95	28.4	0.006	1.802 (1.178-2.757)
Normal-High	74	58.3	239	71.6		
Globulin Level						
High	17	56.7	104	47.1	0.323	1.471 (0.682-3.174)
Low-Normal	13	43.3	117	52.9		
A/G Ratio						
Low	15	50	93	42.1	0.676	1.376 (0.641-2.954)
Normal-High	15	50	128	7.9		

For the same 251 patients with A/G ratio data, a low A/G ratio (<1.0) was observed in 50.0% of PTB patients and 42.1% of EPTB patients (Table 2). Normal-to-high A/G ratio (≥1.0) was present in 57.9% of EPTB patients and 50.0% of PTB patients. The Chi-square test showed p = 0.676, indicating no statistically significant relationship between the A/G ratio and TB type. The prevalence ratio was 1.376 (95% CI: 0.641–2.954), suggesting a weak and nonsignificant association.

4. Discussion

Patients Characteristics

This study analyzed 461 adult tuberculosis patients, comprising 334 pulmonary TB (PTB) cases and 127 extrapulmonary TB (EPTB) cases. While TB is often reported to predominantly affect individuals of productive age due to higher mobility, social interaction, occupational exposure, and stress-related immune compromise,[19] the largest proportion of patients in this study were aged ≥45 years. The 31–44-year age group accounted for 25% of cases, which is lower than expected based on previous reports. This discrepancy may reflect local demographic characteristics or referral patterns at a tertiary hospital where older patients with comorbidities are overrepresented. Male patients represented the majority (57%), supporting prior evidence that men are at higher risk of TB, potentially due to increased environmental exposure, smoking habits, and occupational factors.[20] These sociodemographic characteristics, while informative, are not the primary focus of this study and should be interpreted as descriptive context rather than explanatory findings.

Regarding nutritional status, most patients were classified as having normal nutrition, despite some underweight individuals. This may explain the lack of a strong statistical association between malnutrition and TB in this cohort. Malnutrition has been shown to impair cellular immunity, particularly T-lymphocyte responses, increasing susceptibility to Mycobacterium tuberculosis infection and disease progression.[21] Low educational attainment was observed in a notable proportion of patients, highlighting the importance of education in shaping health literacy, disease awareness, and preventive behavior against tuberculosis. [22]

Association Between Serum Albumin and Globulin Levels and TB Type

This study demonstrated a significant association between serum albumin levels and TB type, with low serum albumin showing a prevalence ratio of 1.802 (95% CI: 1.178–2.757) for being in the EPTB group compared to the PTB group. However, this association must be interpreted cautiously. Albumin is a negative acute-phase protein whose synthesis in the liver is downregulated by proinflammatory cytokines, particularly interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β).[7] These cytokines are elevated in both PTB and EPTB, but patients with extrapulmonary involvement may experience a more prolonged or intense systemic inflammatory state, potentially leading to more pronounced hypoalbuminemia. Additionally, lower albumin levels may reflect poorer nutritional status, which is known to impair cellular immunity and increase susceptibility to disseminated disease.[21]

Nevertheless, it would be an overinterpretation to claim that albumin specifically predicts EPTB location. Low albumin is a non-specific marker of systemic inflammation, nutritional depletion, and chronic illness burden, all of which may be more severe in EPTB patients due to delayed diagnosis or more widespread disease.[15,16] Consistent with a large cohort study in HIV patients, low serum albumin is associated with TB presence and mortality risk, but not specifically with anatomical disease site.[23] Therefore, serum albumin should be positioned as a marker of overall clinical and inflammatory status rather than a site-specific diagnostic indicator for EPTB.

No significant association was observed between serum globulin levels and TB type. This finding contrasts with previous studies reporting higher immunoglobulin levels (particularly IgG and IgA) in EPTB, reflecting a stronger humoral immune response in disseminated or severe forms of disease.[15,16] However, the absence of a statistically significant association in this study does not necessarily imply that no such relationship exists. A critical methodological limitation must be emphasized: globulin data were available for only 251 of 461 patients (54.4%), substantially reducing statistical power to detect a true difference. The wide confidence intervals for the globulin PR (0.682–3.174) further indicate imprecision, and the non-significant p-value (0.323) may reflect type II error rather than a genuine absence of biological association. [24]

Similarly, no significant association was found between the A/G ratio and TB type. Previous studies using serum protein electrophoresis have shown that active TB generally associates with a reduced A/G ratio due to low albumin and elevated gamma globulins, with gradual normalization during treatment.[18] These changes reflect systemic inflammation and immune activation rather than TB-type–specific differences.[11] The lack of association in this study may again be influenced by missing data (same subset of 251 patients) and the absence of multivariable adjustment. It is also possible that the A/G ratio, as a composite measure, loses discriminatory power because both low albumin and high globulin—while individually informative—can occur in both PTB and EPTB with considerable overlap.

Several important limitations must be acknowledged. First, this study employed a retrospective cross-sectional design, relying on medical record completeness and accuracy. Important information on nutritional history, concurrent infections (including HIV), diabetes, or other inflammatory conditions was not consistently available and could not be fully controlled. Second, the reported prevalence ratios are unadjusted associations; no multivariable analysis was performed to account for potential confounders such as age, sex, nutritional status, or comorbidities. Consequently, the observed association between low albumin and EPTB may be confounded by factors that influence both albumin levels and disease severity. Third, missing data for globulin and A/G ratio (only 54.4% of the total sample) substantially reduced statistical power, increasing the risk of type II error and limiting the interpretability of non-significant findings. Fourth, serum albumin, globulin, and A/G ratio were measured at a single time point at initial diagnosis, preventing assessment of dynamic changes over the disease course or in response to treatment. Fifth, the study population was restricted to adult patients at a single tertiary referral center (RSMH Palembang), which limits generalizability to primary care settings or other regions with different demographic and epidemiological profiles. Finally, the cross-sectional design precludes any causal inference; associations should be interpreted as reflecting prevalence differences, not risk or causation.

5. Conclusion

This cross-sectional study found a significant association between low serum albumin levels and extrapulmonary tuberculosis among adult patients at Dr. Mohammad Hoesin Hospital, Palembang. However, given the retrospective design, potential confounding factors (e.g., nutritional status, comorbidities), and the absence of multivariable adjustment, this association should be interpreted as exploratory rather than confirmatory. Serum albumin may have potential as a supplementary clinical indicator reflecting systemic inflammation and disease burden in tuberculosis, but it cannot serve as a standalone or site-specific diagnostic marker.

In contrast, serum globulin levels and the albumin/globulin ratio were not significantly associated with tuberculosis type in this study. These null findings may have been influenced by substantial missing data (only 54.4% of patients had globulin measurements) and limited statistical power; therefore, they do not conclusively rule out a biological relationship.

Given the limitations of the present study, including its cross-sectional nature, single-center setting, unadjusted bivariate analysis, and incomplete laboratory data, the findings should be considered hypothesis-generating rather than definitive. Prospective, multicenter studies with larger sample sizes, standardized laboratory protocols, and multivariable analysis (e.g., log-binomial or Poisson regression to obtain adjusted prevalence ratios) are warranted to validate whether serum albumin independently associates with extrapulmonary tuberculosis after controlling for confounders. Future research should also examine longitudinal changes in serum protein levels during anti-TB treatment to assess their prognostic significance and explore whether combining albumin with other inflammatory markers improves clinical utility.

6. Author Contribution

All authors contributed to the conception and design of the study, data collection, analysis and interpretation, and manuscript preparation. All authors have reviewed and approved the final manuscript.

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