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Relationship between serum matrix Metalloproteinase-9 levels and severity of multibacillary leprosy in patients aged 30 years and under

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Abstract

Background: Leprosy presents a spectrum of immunological responses linked to pathological and clinical manifestations. Matrix Metalloproteinase-9 (MMP-9), an enzyme involved in extracellular matrix degradation and inflammation, has been implicated in cellular immunity. However, the relationship between MMP-9 levels and bacterial load in multibacillary (MB) leprosy remains incompletely understood, particularly across different age groups. **Objective:** To analyze the relationship between serum MMP-9 levels and Bacterial Index (BI) severity in MB leprosy patients, stratified by age groups. **Methods:** A cross-sectional comparative study was conducted from October 2017 to September 2018 at Dr. Rivai Abdullah Leprosy Hospital and Sukajadi Community Health Center, South Sumatra, Indonesia. Thirty-two newly diagnosed or recurrent MB leprosy patients were enrolled via consecutive sampling. Serum MMP-9 levels were measured using ELISA, and disease severity was classified by BI (<3 vs ≥3) using Slit Skin Smear. Data were analyzed using unpaired t-tests and Kruskal-Wallis tests, with significance set at $P<0.05$. **Results:** Age group and marital status significantly influenced BI severity ($P<0.05$). Among patients aged <30 years, those with BI≥3 had significantly lower serum MMP-9 levels (2101.44±430.02 ng/L) compared to BI<3 (2621.57±469.37 ng/L; $P=0.044$). In patients aged ≥30 years, MMP-9 levels were lower in BI≥3 group (1770.19±477.21 ng/L vs 2068.67±550.58 ng/L), but this difference was not statistically significant ($P>0.05$). **Conclusion:** Lower serum MMP-9 levels in severe MB leprosy may reflect diminished cell-mediated immunity. The significant inverse relationship between MMP-9 and BI in younger patients suggests age-dependent immunological variations. These findings support MMP-9 as a potential biomarker for disease severity assessment in MB leprosy.

Keywords: Leprosy, multibacillary; matrix metalloproteinase 9; bacterial load; cell-mediated immunity; biomarkers; age factors

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INTRODUCTION

Leprosy, or Hansen's disease, remains a significant chronic neglected tropical disease (NTD) and a leading cause of infection-related disability worldwide. Caused by *Mycobacterium leprae*, the disease primarily affects skin and peripheral nerves, leading to sensory loss and tissue damage from repeated injury [1]. In 2019, over 200,000 new cases were reported from more than 100 countries, with Brazil, India, and Indonesia accounting for approximately 80% of the global burden2. Delayed diagnosis frequently results in permanent nerve damage and disability, while persistent stigma creates substantial barriers to treatment-seeking and social support [2,3].

The immunological characteristics of the host exert greater influence on disease pathology than intrinsic bacterial mechanisms. Leprosy presents an immunological spectrum closely correlated with pathological and clinical manifestations, as well as bacterial burden [4]. Patients with robust cell-mediated immunity (CMI)—characterized by few bacilli, relative resistance to pathogens, and predominant Th1 cytokine expression with localized infection, central hypopigmentation, and hypoesthesia—are classified as paucibacillary (PB) leprosy. Conversely, patients with defective CMI exhibit no apparent resistance to *M. leprae*, numerous poorly demarcated elevated nodular lesions across most body regions, and foamy macrophages in the dermal layer, and are classified as multibacillary (MB) leprosy. The mechanisms underlying T cell hyporesponsiveness and clonal anergy in MB leprosy patients with high bacterial indices remain poorly understood [5].

Slit Skin Smear (SSS) remains the gold standard for accurate diagnosis. Sample sites typically include active lesions, areas with differential sensitivity, and the earlobe and contralateral elbow. This bacterioscopic examination demonstrates 100% specificity and 50% sensitivity [6]. Despite low sensitivity (10-50%, dependent on laboratory personnel expertise), SSS maintains its position as the diagnostic gold standard due to near-perfect specificity. Furthermore, SSS provides insights into *M. leprae* distribution in skin, enabling assessment of infectivity and disease severity. Skin smears facilitate diagnosis, classification, treatment monitoring, and severity evaluation. All smear-positive patients are classified and treated as MB leprosy. Leprosy reactions occur more frequently in patients with elevated BI [7].

Assessment of immune response and inflammatory processes in leprosy patients represents a critical area of investigation for understanding disease pathogenesis. Matrix Metalloproteinase-9 (MMP-9), an enzyme involved in extracellular matrix degradation, plays a significant role in inflammation and tissue damage [8]. MMP-9 is produced by keratinocytes, monocytes, and macrophages, and serves as the primary

MMP secreted by monocytes, responsible for T cell and dendritic cell migration. MMP-9 contributes to fibrosis in late-stage neuritic leprosy, impeding nerve fiber regeneration and rendering leprosy nerve damage irreversible even after infection resolution. Teles et al. investigated MMP-9 function in leprosy by comparing MMP-9 mRNA levels in lesions and serum, finding higher levels in tuberculoid versus lepromatous lesions. Singh et al. and Youssef et al. support the hypothesis that MMP-9 serves as a marker of active CMI in leprosy patients. Intense MMP-9 immunoreactivity was observed in epithelioid cell granulomas of newly diagnosed TT and BT leprosy compared to mild-to-moderate immunoreactivity in MB leprosy patients [9].

The relationship between BI and serum MMP-9 levels in MB leprosy patients remains incompletely understood. Research addressing this gap is essential for elucidating disease pathogenesis mechanisms, predicting severity levels, and supporting the development of more effective diagnostic and therapeutic strategies. Therefore, this study aimed to analyze the relationship between BI and serum MMP-9 levels in MB leprosy patients. The findings are expected to contribute scientific knowledge to healthcare, particularly in leprosy management and treatment.

METHODS

Study design and setting

This observational cross-sectional comparative study was conducted from October 2017 to September 2018 at two healthcare facilities in South Sumatra Province, Indonesia: the outpatient clinic of Dr. Rivai Abdullah Leprosy Hospital and Sukajadi Community Health Center. Laboratory analyses, including Bacterial Index (BI) determination and enzyme-linked immunosorbent assay (ELISA) for Matrix Metalloproteinase-9 (MMP-9), were performed at designated provincial laboratories.

Population, sample size, and sampling technique

The study population comprised newly diagnosed or recurrent MB leprosy patients and household contacts (nara kontak) who had resided with patients for ≥5 years. Sample size calculation employed a two-proportion hypothesis test formula with 80% power and 95% confidence level (α=0.05), yielding a minimum requirement of 28 patients and 28 controls. Participants were recruited through consecutive sampling, enrolling eligible individuals sequentially until the target sample size was achieved. Consecutive sampling was selected to enhance feasibility and representativeness of the accessible population during the study period.

Inclusion and exclusion criteria

Inclusion criteria required participants to be adults aged 18-60 years with confirmed MB leprosy (positive Slit Skin Smear) and willing to provide written informed consent. Exclusion criteria eliminated individuals with severe comorbidities (e.g., diabetes mellitus, systemic lupus erythematosus), pregnant or lactating women, or those with critical illness that could confound study results or compromise participant safety.

Study variables and measurements

The independent variable was serum MMP-9 level (µg/mL), quantified using ELISA (Human MMP-9 ELISA Kit, Bioassay Technology Laboratory). The dependent variable was leprosy severity, classified by BI as mild (BI<3) or severe (BI≥3) using Slit Skin Smear and Ridley's logarithmic scale. Covariates included age group (ordinal), sex

(nominal), marital status (nominal), educational level (ordinal), and occupation (categorical).

Research procedures

Following informed consent acquisition, venous blood samples (5 mL) were collected aseptically from each participant. Samples underwent centrifugation for serum separation and were stored at -60°C until analysis. MMP-9 quantification followed standardized ELISA protocols per manufacturer guidelines. BI determination employed Ziehl-Nielsen staining of slit skin smears collected from earlobe and active lesion sites.

Instruments and data collection

Data collection instruments included structured questionnaires for demographic and clinical information, standardized ELISA kits for MMP-9 measurement with documented sensitivity and specificity, and Slit Skin Smear examination equipment. Quality assurance protocols encompassed pre-analytical (proper sample collection, transportation, storage), analytical (equipment calibration, test replication), and post-analytical (data verification, documentation) phases.

Data extraction and statistical analysis

Data normality was assessed using the Shapiro-Wilk test. Normally distributed data were analyzed with parametric tests (unpaired samples t-test), while non-normal data underwent log10 transformation or non-parametric tests (Kruskal-Wallis test). Associations between MMP-9 levels, BI severity, and covariates were evaluated using appropriate statistical tests. Statistical significance was defined as $P<0.05$. Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical considerations

Ethical approval was obtained from the National Research Ethics Commission of Andalas University (approval number: 531/KEP/FK/2017). Written informed consent was secured from all participants prior to enrollment. Participant confidentiality was strictly maintained through data anonymization and secure storage protocols. Study procedures adhered to the Declaration of Helsinki principles.

RESULTS

This study enrolled 32 participants with multibacillary leprosy, comprising 14 individuals with BI<3 and 18 individuals with BI≥3. Baseline characteristics are presented in Table 1. Age group and marital status demonstrated statistically significant associations with higher BI values, indicating that severe multibacillary leprosy occurred more frequently in older individuals and married participants (Table 1). Mean serum MMP-9 levels stratified by age group and BI severity are presented in Table 2. Among participants aged <30 years, those with BI<3 exhibited mean MMP-9 levels of 2621.57±469.37 ng/L, significantly higher than those with BI≥3 (2101.44±430.02 ng/L; P=0.044). In participants aged ≥30 years, mean MMP-9 levels were 2068.67±550.58 ng/L for BI<3 and 1770.19±477.21 ng/L for BI≥3. While MMP-9 levels were lower in the severe BI group across both age strata, the difference achieved statistical significance only in the younger age group.

Table 1. Baseline characteristics of study participants by bacterial index severity

Parameter	IB < 3 (n = 14)*	IB ≥ 3 (n = 18)*	p-value**
Age Group (years old)			
<20	3 (21.4%)	2 (11.1%)	**0.028**
21-30	4 (28.6%)	5 (27.8%)	
31-40	5 (35.7%)	5 (27.8%)	
41-50	0 (0.0%)	6 (33.3%)	
51-60	2 (14.3%)	0 (0.0%)	
Marital Status			
Married	4 (28.6%)	12 (66.7%)	**0.033**
Not Married	10 (71.4%)	6 (33.3%)	
Gender			
Male	12 (85.7%)	15 (83.3%)	0.854
Female	2 (14.3%)	3 (16.7%)	
Education			
Elementary School	7 (50.0%)	9 (50.0%)	0.881
Junior High School	3 (21.4%)	5 (27.8%)	
Senior High School	4 (28.6%)	4 (22.2%)	
Occupation			
Unemployed	1 (7.1%)	3 (16.7%)	0.739
Housewife	0 (0.0%)	1 (5.6%)	
Laborer	4 (28.6%)	5 (27.8%)	
Farmer	5 (35.7%)	6 (33.3%)	
Enterpreneur	3 (21.4%)	3 (16.7%)	
Student	1 (7.1%)	0 (0.0%)	
MMP-9 (µg/mL)	1921 (1701 – 4374)	1793 (1180 – 2907)	0.129

Table 2. Serum MMP-9 levels by age group and bacterial index severity

Controled Variables	IB < 3*	IB ≥ 3*	P Value**
Marital Status			
Married	2531 ± 1233.0	1860 ± 495.8	0.360
Not Married	1877 (1701 – 4204)	1770 (1273 – 2127)	0.193
Age Group			
<30	2495 ± 716.2	1705 ± 399.1	**0.044**
31-60	2259 ± 966.3	1883 ± 477.2	0.284

*Data are presented as mean ± SD when normally distributed and median (min-max) when not normally distributed. Normality was tested using the Shapiro-Wilk test. **P values were calculated using the unpaired t-test when data were normally distributed and the Mann-Whitney U test for data that were not normally distributed.

DISCUSSION

This study demonstrated an inverse relationship between serum MMP-9 levels and BI severity in MB leprosy patients, with statistical significance observed in the younger age group (<30 years). Lower MMP-9 levels in severe MB leprosy likely reflect

diffuse macrophage infiltration replete with bacilli and the absence of specific cellular immune responses to *M. leprae*. The dominant interleukin-4 (IL-4) response in MB leprosy has been reported to suppress MMP-9 production, associated with IL-4's capacity to inhibit prostaglandin E2 (PGE2) synthesis [10,11].

Previous investigations support MMP-9's role as a biomarker of active CMI in leprosy. Singh et al. and Youssef et al. demonstrated intense MMP-9 immunoreactivity in epithelioid cell granulomas of tuberculoid and borderline-tuberculoid leprosy, contrasting with mild-to-moderate immunoreactivity in MB leprosy patients9,10. Teles et al. reported elevated MMP-9 mRNA levels in tuberculoid lesions compared to lepromatous lesions, supporting the association between robust CMI and increased MMP-9 expression [12]. These findings align with our observation of reduced MMP-9 levels in severe MB leprosy, reflecting impaired cellular immunity.

The mechanistic basis for MMP-9 suppression in MB leprosy involves the predominant Th2 cytokine profile, particularly IL-4. Chizzolini et al. demonstrated that Th2 cell membrane factors, in association with IL-4, enhance MMP-1 production while decreasing MMP-9 synthesis in granulocyte-macrophage colony-stimulating factor (GM-CSF)-differentiated human monocytes [13]. Furthermore, Corcoran et al. established that IL-4 inhibits PGE2 synthesis, subsequently blocking both interstitial collagenase and 92-kDa type IV collagenase/gelatinase (MMP-9) production by human monocytes [14]. This immunoregulatory mechanism explains the diminished MMP-9 levels observed in severe MB leprosy characterized by high bacterial loads and defective CMI.

The significant inverse correlation between MMP-9 and BI in younger participants (<30 years) but not in older individuals (≥30 years) suggests age-dependent modulation of immune responses. Aging is characterized by increased protein cross-linking and formation of aggregates resistant to proteolytic enzyme activity, leading to accumulation. While the precise mechanisms of organismal aging remain incompletely understood, substantial evidence indicates proteolytic enzyme involvement in age-related pathology [15].

Serine proteases, including plasmin, trypsin, and elastase, contain highly reactive serine residues. Plasmin intensifies extracellular matrix protein degradation directly and indirectly through MMP-3, MMP-9, MMP-1, and MMP-2 activation. Accumulation of plasmin degradation products and extracellular vascular wall matrix breakdown contributes to vascular aging pathogenesis. Elevated plasmin-α2-antiplasmin complex concentrations have been observed during aging and in individuals with acute coronary syndrome. Current and prior findings indicate increased plasma plasmin activity reflects heightened coagulation and fibrinolysis activation, potentially serving as markers of atheromatosis progression and cardiovascular disease, both characteristic of advanced age [15].

Trypsin, synthesized by pancreatic exocrine tissue as a proenzyme, associates with α1-antitrypsin and α2-macroglobulin protease inhibitors in serum. The trypsin-α2-macroglobulin complex resists degradation by other proteases while maintaining enzymatic activity. Trypsin hydrolyzes dietary proteins and extracellular matrix proteins, indirectly activating latent forms of numerous MMPs, including MMP-9, MMP-8, and MMP-1. Age-related increases in α1-antitrypsin concentration inhibit serum elastase activity. Middle-aged groups demonstrate statistically higher trypsin activity compared to elderly groups. Studies assessing age-dependent trypsin activity in brain structures have identified decreased trypsin activity with advancing age in cortex, cerebellum, striatum, and paleglobe of aged rats and mice compared to young

animals. The age-related decline in serum trypsin activity may arise from increased α1-antitrypsin activity, a serine protease inhibitor [15].

Based on recent literature and current findings, decreased serum elastase activity (comparing middle-aged and elderly groups) and increased serine protease inhibitor concentrations may serve as markers of inflammatory changes in arterial vascular walls. These alterations characterize atheromatosis, a chronic process developing with advancing age. The diminished significance of MMP-9-BI associations in older participants may reflect this age-related proteolytic enzyme modulation, attenuating the discriminatory capacity of MMP-9 as a severity marker in aged populations.

Clinical and research implications

These findings support the potential utility of serum MMP-9 as a biomarker for disease severity assessment in MB leprosy, particularly in younger patient populations. The inverse relationship between MMP-9 levels and bacterial load reflects underlying immunological status and may facilitate risk stratification for complications such as leprosy reactions and nerve damage. Future prospective studies should evaluate MMP-9's predictive value for treatment response and reaction development, potentially informing personalized management strategies.

The age-dependent variation in MMP-9-BI associations warrants further investigation into age-specific immunological mechanisms in leprosy pathogenesis. Understanding these variations may guide age-stratified approaches to diagnosis, prognosis, and treatment monitoring. Additionally, the role of age-related proteolytic enzyme modulation in infectious disease susceptibility and severity represents an important area for future research.

Limitations

Several limitations should be considered when interpreting these results. The cross-sectional design precludes causal inference regarding the temporal relationship between MMP-9 levels and disease severity. The relatively modest sample size, particularly when stratified by age groups, may limit statistical power and generalizability. Consecutive sampling, while pragmatic, may introduce selection bias compared to random sampling approaches. The study did not assess other MMPs or inflammatory mediators that may contribute to disease pathogenesis, limiting comprehensive understanding of the immunological milieu. Longitudinal studies with larger, more diverse populations are needed to validate these findings and explore their clinical applicability.

CONCLUSIONS

Lower serum MMP-9 levels in severe multibacillary leprosy likely result from diffuse macrophage infiltration laden with bacilli and absent specific cellular immune responses to *M. leprae*. Dominant IL-4 in MB leprosy suppresses MMP-9 production through PGE2 synthesis inhibition. Active MMP-9 concentration declines with increasing age due to elevated plasmin activity and α1-antitrypsin (serine protease inhibitor) concentrations. The significant inverse relationship between MMP-9 and bacterial load in younger patients suggests potential utility as an age-stratified biomarker for MB leprosy severity assessment. Future investigations should employ prospective longitudinal designs with larger, geographically diverse cohorts to validate MMP-9's prognostic value across different populations and disease stages. Studies should comprehensively assess multiple MMPs, tissue inhibitors of metalloproteinases

(TIMPs), and related inflammatory mediators to elucidate the complete immunological profile underlying leprosy severity. Age-stratified analyses incorporating detailed assessments of proteolytic enzyme systems and their inhibitors would clarify age-dependent immunological variations. Evaluation of MMP-9's predictive capacity for treatment response, leprosy reactions, and nerve damage could establish its clinical utility in personalized medicine approaches. Mechanistic studies investigating IL-4-mediated MMP-9 suppression pathways may identify therapeutic targets for modulating disease progression and complications.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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