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# Relationship of Matrix Metalloproteinase-1 with Clinical and Radiological Features of Pulmonary Tuberculosis Co-infection of Human Immunodeficiency Virus Patients

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***Abstract***
***Introduction:*** *The co-infection of pulmonary Tuberculosis (TB) in Human Immunodeficiency Virus (HIV) patients continues to pose a global health challenge. Mycobacterium tuberculosis (Mtb) and HIV can synergize, thereby worsening the condition of patients. Matrix metalloproteinase (MMP) is known to play a role in the pathogenesis of HIV-TB. Clinical and radiological presentations of M. tuberculosis patients show destruction of the extracellular matrix of the lungs involving protease actions, particularly matrix metalloproteinases (MMPs), one of which is MMP-1, resulting in the degradation of the lung's structural fibrils.* ***Objective:*** *The aim of this study is to investigate the relationship between MMP-1 and the clinical and radiological manifestations in the co-infection of pulmonary TB in HIV patients.* ***Method:*** *The research sample comprised 34 individuals. The median age of the study subjects was 41.5 (21 – 67) years, with the majority being <50 years old (64.7%) and male (70.6%).* ***Result and Discussion:*** *The cut-off value for MMP-1 level was determined using ROC curve analysis, where a level of 2.125 pg/mL demonstrated good sensitivity and specificity in predicting clinical symptoms and radiological findings. Mann-Whitney test revealed a significant difference in MMP-1 levels between positive and negative groups for both clinical symptoms ($p<0.05$) and radiological findings ($p<0.01$). Fisher's Exact test supported the association between MMP-1 levels and clinical symptoms (PR=1.929; CI95%=0.864 – 4.306; p=0.012) as well as radiological findings (PR=5.571; CI95%=0.928 – 33.441; $p<0.001$). Multivariate analysis indicated that variables other than MMP-1 level did not influence clinical symptoms and radiological findings in this study.* ***Conclusion:*** *In conclusion, MMP-1 levels are associated with clinical symptoms and radiological features of pulmonary TB coinfection in HIV patients. The MMP-1 cutoff level of 2.125 pg/mL increases the risk of clinical symptoms and radiological findings in patients*
***Keyword: Pulmonary Tuberculosis; Matrix Metalloproteinase; HIV;***

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## Introduction

HIV - Pulmonary TB coinfection is currently a major health problem throughout the world and the main focus of discussions on health issues at the global level The World Health Organization (WHO) is currently HIV co-infection (Human Immunodeficiency Virus) – Pulmonary TB (Tuberculosis). Both infections are among the ten leading causes of death worldwide. In Indonesia, accumulatively based on data from the Ministry of Health of the Republic of Indonesia in 2021 reached 732,436 people tested for HIV. In the HIV/AIDS information report (Acquired Immune deficiency Syndrome) & Pulmonary TB for the Third Quarter Period (July-September) 2021 reported. Bali is the province with the fifth highest number of cases in Indonesia with 9,125 cases (UNAIDS, 2021).

The combination of these two infectious diseases influences each other in all aspects of the disease, starting from pathogenesis, epidemiology, clinical manifestations, treatment and prevention, and can even influence larger issues such as social, economic and political consequences (Silitonga, Kurniati, Ariza, & Imanto, 2019). The chance of developing pulmonary TB infection is up to 18 times higher in people living with HIV.

In individuals who host two pathogens, Mycobacterium tuberculosis (Mtb) and HIV increase each other's potency and accelerate the decline in immunological function (Bell & Noursadeghi, 2018)

Studies show that Mtb influences the process of HIV infection and replication by providing a favorable environment for HIV growth, namely by increasing activity coreceptor CXCR4 (C-X-C Chemokine Receptor type 4) and CCR5 (Chemocine CoReceptor 5) increases proinflammatory cytokines and decreases CCL5(C-X-C Motif Chemokine Ligand 5). Not only that, the body's immune response to micro bacteria This can also help the HIV replication process, like TNF in response to pulmonary TB can initiate transcription of cells infected with HIV so that HIV can replicate. Likewise with HIV, when HIV attacks the body's immune cells such as CD4, CD8 it will cause a decrease in the body's immune activity. When this happens, when the body comes into contact with Mtb or experiences reactivation, the ability of the body's immune cells to neutralize antigens fails, resulting in active Mtb infection (Silitonga et al., 2019)

The clinical and radiological features of patients with pulmonary TB co-infection with HIV, initially form granulomas which are the body's typical immune response to pathogens. In the center of tuberculous granulomas, caseous necrosis can occur which will be surrounded by activated macrophages, T cells and fibroblasts. Caseous material is rich in lipids and comes from dead macrophages. In cases, Mtb promotes the destruction of the extracellular matrix of the lung spreading from the interstitium to the airways, causing the formation of cavities (cavities) which are sites where Mtb immunodeficiency can reproduce. Cavity formation involves the action of proteases, particularly MMPs (Matrix Metalloproteinases), which is able to degrade lung structural fibrils (Bell & Noursadeghi, 2018)

MMPs are enzymes that play a role in tissue damage and the spread of disease. MMP plays a role in degrade extracellular matrix and basement membrane (Kathamuthu et al., 2020). Various studies have proven the upregulation of MMPs in response to Mtb infection. Cavity formation must involve proteases, especially MMPs which are capable of degrading the lung fibril structure viz Matrix Metalloproteinase-1 (MMP-1). Clinical studies of patients with pulmonary TB yielded the strongest evidence implicating MMP-1 in lung matrix destruction. Consistent with a central role for MMP-1 in pulmonary TB-mediated tissue destruction, transgenic expression of human MMP-1 in an animal model namely mice causes increased collagen destruction in TB granulomas (Elkington et al., 2011)

HIV-TB pulmonary infection can affect matrix levels metalloproteinase 1 (MMP-1), a proteolytic enzyme involved in remodeling the extracellular matrix in lung tissue. Several factors that can influence MMP-1 levels in HIV co-infection with pulmonary TB include: HIV virus activity, co-infection tuberculosis lungs, immune status, antiretroviral therapy (ARV), anti-tuberculosis drugs (OAT), genetic polymorphism (Rammaertet al, 2019)

At neutral pH, MMP-1 is the most powerful enzyme in degrading type I collagen resulting in an increase in lung tension. Matrixmetalloproteinase1 is associated with increased activity and has been associated with more massive radiological changes and cavity formation in pulmonary TB sufferers. This shows that MMP-1 is one of the main mediators of lung tissue damage in TB. However, in coinfection HIV TB There is still limited research data showing the relationship of MMPs, especially MMP-1, to clinical symptoms and radiological images (O'Kane et al., 2010)

In the Elkington Studyet al. (2019) evaluating the role of MMPs in pulmonary TB immunopathology found that MMP-1 concentrations increased significantly in pulmonary TB patients with HIV and non-HIV ($p<0.05$), while TIMP concentrations (Tissue Inhibitor of Metalloproteinase) are lower in non-HIV pulmonary TB patients. Testing on human monocytes in the study also showed Mtb infection selectively increases the expression and secretion of MMP-1 and Ro32-3555 genes which are specific MMPs inhibitors thereby suppressing MMP-1 activity activated by Mtb (Elkington et al., 2011)

On Study Tadokera et al. (Rohlwink et al., 2019) measured MMPs protein levels in the serum of HIV-TB patients associated immune reconstitution inflammatory syndrome (TB-IRIS) and control. The results of this study showed that there was an increase in MMP-1, -3, -7, and -10 transcript levels in TB-IRIS patients compared to controls at 6 or 24 hours. Similarly, secretion of these proteins in stimulated cultures was higher in TB-IRIS than in controls. Among the types of MMP, MMP-1 has an important role in lung cavity formation associated with Mtb infection. However, research regarding MMP-1 in relation to the clinical and radiological features of pulmonary HIV-TB in Indonesia is still rare. So researchers are interested in studying specifically the relationship between MMP-1 levels and the clinical and radiological features of pulmonary HIV-TB co-infected patients (Rohlwink et al., 2019)

## Method

This study is an analytical observational study using a cross-sectional research design or design. Cross-sectional research is a type of research in which measurements and observations of variables are carried out only once, at a time. The cross-sectional design was chosen to determine the relationship between MMP-1 and the clinical and radiological features of HIV-TB Pulmonary patients. This study began with screening research samples then examining MMP-1 levels and observing the clinical and radiological features of HIV-Pulmonary TB patients. To determine the relationship between these variables in a certain period using primary data from the results of direct examination of MMP-1 levels of patients and interview formulars as well as secondary data obtained from patient medical records

## Result and Discussions

### Result

### Basic Characteristics of the Sample

This study is an analytical cross-sectional study with the number of samples selected based on inclusion and exclusion criteria, and involved in the analysis, namely 34 samples. Based on the results of the study, the median age of the study sample was around 41.5 years with the majority aged <50 years (64.7%). Gender was found to be mostly male (70.6%). Most were advanced (79.4%) with a median CD4 cell level of 88 (3-432) cells/mm3 (see Table 1)

Most of the study sample showed at least one of the clinical symptoms (88.2%) such as weight loss (85.3%), bloody cough (8.8%), tightness (20.6%) and night sweats (8.8%). Most of the study samples showed at least one radiological picture pointing to HIVTB lung coinfection (79.4%) with infiltrate images (35.3%), fibrosis (29.4%), cavitation (11.8%) and pleural effusion (29.4%). MMP-1 levels as an independent variable in this study were at a median of 2.85 (1.19 – 63.11) pg/mL.

**Table 1**
Characteristics of the Research Subject

| Variable | Value/Frequency N = 34 |
|---|---|
| Age (years), median (min-max) | 41,5 (21 – 67) |
| Age<br>≥50 years<br><50 years | 12 (35,3)<br>22 (64,7) |
| Gender, n (%) | |
| Man | 24 (70,6) |
| Woman | 10 (29,4) |
| Clinical Stage, n (%)<br>Early Stage | 7 (20,6) |
| Advanced Stage | 27 (79,4) |
| CD4 Levels (sell/mm$^3$), median (min-max) | 88 (3 - 432) |
| CD4 Levels<br><200 sell/mm$^3$<br>≥200 sell/mm$^3$ | 24 (70,6)<br>10 (29,4) |
| Clinical symptoms, n (%) Yes | 30 (88,2) |
| Losing Weight, n (%) | 26 (96,2) |
| Coughing up blood, n (%) | 3 (11,1) |
| Shortness of breath, n (%) | 7 (25,9) |
| Hypoglycaemia, n (%) | 3 (11,1) |
| No | 4 (11,8) |
| Radiological Overview, n (%) Yes | 27(79,4) |
| Infiltrates, n (%) | 12 (44,4) |
| Fibrosis, n (%) | 10(37,0) |
| Cavities, n (%) | 4(14,8) |
| Pleural effusion, n (%) | 10 (37) |
| No | 7 (20,6) |

**ROC Curve Analysis of MMP Levels on Clinical Symptoms and Radiological Features**

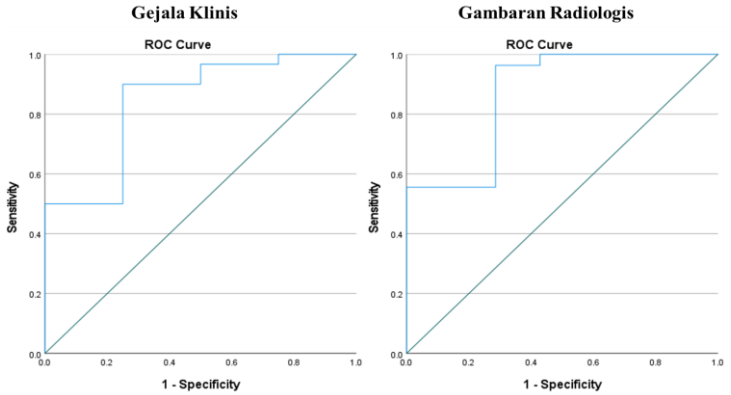


**Figure 1**

**Table 2**
Cut-off Value of MMP-1 Levels Against Clinical Symptoms and Radiological Features

| | Area Under Curve (AUC) | P-value | Cut-off Value | Sensitivity | Specificity |
|---|---|---|---|---|---|
| Clinical symptoms | 0,842 | 0,028* | 2,125 | 0,900 | 0,750 |
| Radiological Overview | 0,868 | 0,003* | 2,125 | 0,963 | 0,714 |

*Results are considered significant if $p \leq 0.05$.

## Analysis of the Relationship of MMP-1 Levels to Clinical Symptoms and Radiological Features by Cross-Tabulation of MMP-1 Levels Cut-off

Based on the latest cut-off value that has been determined, the analysis of the relationship between MMP-1 levels with clinical symptoms and radiological features of HIV-TB Lung coinfection can be assessed based on the prevalence ratio (PR) with the Fisherexact test. The results of this bivariate analysis test showed MMP-1 levels of >2.125 pg/mL showed a relationship between MMP-1 levels to clinical symptoms and Radiological picture of HIV-TB lung co-infection (Table 3).

**Table 3**
Cross-tabulation of the Relationship of MMP-1 Levels to Clinical Symptoms and Features Radiological

| MMP-1 levels | Clinical symptoms | | | PR Value | P value | IK95% |
|---|---|---|---|---|---|---|
| | Yes | No | Total | | | |
| ≥2,125 pg/mL | 27 (96,4%) | 1 (3,6%) | 28 (100,0%) | 1,929 | 0,012* | 0,864-4,306 |
| <2,125 pg/mL | 3 (50,0%) | 3 (50,0%) | 6 (100,0%) | | | |

| MMP-1 Level | Radiological Overview | | | PR Value | P value | IK95% |
|---|---|---|---|---|---|---|
| | Yes | No | Total | | | |
| ≥2,125 pg/mL | 26 (92,9%) | 2 (7,1%) | 28 (100,0%) | 5,571 | <0,001* | 0,928-33,441 |
| <2,125 pg/mL | 1 (16,7%) | 5 (83,3%) | 6 (100,0%) | | | |

* Significant results (p≤0,05)

## Analysis of the Relationship of Other Variables to Clinical Symptoms and Radiological Features

Analysis of the relationship between other variables to clinical symptoms and radiological features was performed using the Fisher Exact test. The results of the variable relationship test on clines symptoms can be seen in Table 4 and on the radiological picture in Table 5. Analysis of the relationship showed that HIV stage, and CD4 levels were significantly associated with clinical symptoms ($p<0.05$). Advanced HIV stages (stages 3 and 4) have a PR value of 2.333 and CD4 levels <200 cells/mm3 have a PR value of 1.667. This is consistent with the theory that advanced HIV staging and low CD4 levels are risk factors for HIV-TB co-infection.

**Table 4**
Results of Analysis of Variable Relationships to Clinical Symptoms

| **Age** | **Clinical symptoms** | | | **PR Value** | **P value** | **IK95%** |
|---|---|---|---|---|---|---|
| | Yes | No | Total | | | |
| ≥50 years | 11 (91,7%) | 1 (8,3%) | 12 (100,0%) | 1,061 | 1,000 | 0,837-1,347 |
| <50 years | 19 (86,4%) | 3 (13,6%) | 22 (100,0%) | | | |
| **Gender** | **Clinical symptoms** | | | **PR Value** | **P value** | **IK95%** |
| | Yes | No | Total | | | |
| Man | 22 (91,7%) | 2 (8,3%) | 24 (100,0%) | 1,146 | 0,564 | 0,822-1,598 |
| Woman | 8 (80,0%) | 2 (20,0%) | 10 (100,0%) | | | |
| **HIV staging** | **Clinical symptoms** | | | **PR Value** | | **IK95%** |
| | Yes | No | Total | | | |
| Advanced Stage | 27 (100,0%) | 0 (0,0%) | 27 (100,0%) | 2,333 | <0,001* | 0,992-5,489 |
| Early Stage | 3 (42,9%) | 4 (57,1%) | 7 (100,0%) | | | |
| **CD4 Levels** | **Clinical symptoms** | | | **PR Value** | **P value** | **IK95%** |
| | Yes | No | Total | | | |
| <200 cells/mm3 | 24 (100,0%) | 0 (0,0%) | 24 (100,0%) | 1,667 | 0,005* | 1,005-2,765 |
| ≥200 cells/mm | 6 (60,0%) | 4 (4,0%) | 10 (100,0%) | | | |

*Analysis was performed using Fisher Exact Test. Results are considered significant if $p \leq 0.05$

Regarding radiological images, relationship analysis shows that the stage HIV and CD4 levels are significantly associated with radiological features ($p<0.05$). Advanced HIV stages (stages 3 and 4) have a PR value of 2,074and CD4 levels <200 cells/mm3 have a PR value of 2.396. It is appropriate with the theory that advanced stages of HIV and low CD4 levels constitute risk factors for HIV-TB coinfection.

**Table 5**

Results of Analysis of the Relationship of Variables to Radiological Images

| **Age** | **Radiological Overview** | | | **PR Value** | **P value** | **IK95%** |
|---|---|---|---|---|---|---|
| | Yes | No | Total | | | |
| ≥50 years | 9 (75,0%) | 3 (25,0%) | 12 (100,0%) | 0,917 | 0,677 | 0,626-1,342 |
| <50 years | 18 (81,8%) | 4 (18,2%) | 22 (100,0%) | | | |
| **Gender** | **Radiological Overview** | | | **PR Value** | **P value** | **IK95%** |
| | Yes | No | Total | | | |
| Man | 20 (83,3%) | 4 (16,7%) | 24 (100,0%) | 1,190 | 0,394 | 0,764-1,855 |
| Woman | 7 (70,0%) | 3 (30,0%) | 10 (100,0%) | | | |
| **HIV staging** | **Radiological Overview** | | | **PR Value** | | **IK95%** |
| | Yes | No | Total | | | |
| Advanced Stage | 24 (88,9%) | 3 (11,1%) | 27 (100,0%) | 2,074 | <0,020* | 0,873-4,930 |
| Early Stage | 3 (42,9%) | 4 (57,1%) | 7 (100,0%) | | | |
| **CD4 Levels** | **Radiological Overview** | | | **PR Value** | **P value** | **IK95%** |
| | Yes | No | Total | | | |
| <200 cells/mm3 | 23 (95,8%) | 1 (4,2%) | 24 (100,0%) | 2,396 | <0,001* | 1,116-5,142 |
| ≥200 cells/mm | 4 (40,0%) | 6 (60,0%) | 10 (100,0%) | | | |

*The analysis was performed using the Fisher Exact Test. Results considered significant (p≤0.05)

## Multivariate Analysis of the Effect of Free Variables on Clinical Symptoms and Radiological Features

Multivariate analysis with logistic regression was performed to assess the effect of other variables such as age, sex, HIV stage and CD4 levels on clinical symptoms and radiological features of HIV-Pulmonary TB co-infection. This analysis is also to assess the independent relationship of the MMP-1 independent variable to clinical symptoms or radiological features. The results of the analysis showed MMP-1 levels as the only variable associated with clinical symptoms or radiological features in the HIV-Pulmonary TB co-infection study sample, thus strengthening its position as an independent variable (see Table 6 and Table 7).

**Table 6**

Multivariate analysis of the effect of independent variables on clinical symptoms

| **Variable** | **Adjusted OR** | **PR Value** | **IK95%** |
|---|---|---|---|
| HIV staging | 0,603 | 0,241 | -0,245 – 0,715 |
| CD4 Levels | -0,005 | 0,978 | -0,238 – 0,232 |
| MMP-1 levels | 0,349 | 0,014* | 0,063 – 0,527 |

*Analysis was performed using logistic regression. The result is considered significant if p≤0.05

**Table 7**
Multivariate analysis of the influence of independent variables on radiological features

| Variable | Adjusted OR | PR Value | IK95% |
|---|---|---|---|
| HIV staging | 0,114 | 0,448 | -0,188 – 0,416 |
| CD4 Levels | 0,264 | 0,123 | -0,067 – 0,537 |
| MMP-1 levels | 0,535 | 0,001* | 0,270 – 0,865 |

*Analysis was performed using logistic regression. The result is considered significant if p≤0.05

## Discussion

### Basic Characteristics of the Sample

The median age of the observed study sample was approximately 41.5 years with the majority aged <50 years (64.7%) and males (70.6%). This finding is in line with the demographic characteristics of patients with HIV-TB Lung coinfection in Bali previously, where patients aged around 39.13±11,734 years were predominantly aged <50 years (76.7%). In addition, the study also received more male patients than female patients (70% vs 30%) (Gayatri & Wulandari, 2023)

Related research in Gresik, Indonesia also shows that HIV-TB Lung Coinfection patients are dominated by men (75%) (Fatimatuzzuhro, Aliyah Siti Sundari, & Dwi Wahyu Indriati, 2020). Regarding age, the Indonesian Ministry of Health also shows similar findings where HIV prevalence is highest in the adult age group (26-45 years) (Kementerian Kesehatan RI, 2022).

The predominance of the research sample was HIV clinical stage IV (64.7%) and a median CD4 count of 88 cells/mm3, indicating further disease progression. These results are in line with previous research where 71.7% of patients were classified as advanced HIV stages (stages 3 and 4) (Gayatri & Wulandari, 2023). This could be related to the results of research by Rockwood, et al. in 2017 which showed that HIV/Mtb co-infected patients had higher levels of heme oxygenase-1, which was inversely correlated with the number of CD4+ T cells and positively correlated with viral load, indicating that HIV coinfection quantitatively reduced the number of CD+ T cells and increases viral load in TB patients (Rockwood et al., 2017)

The clinical symptoms of pulmonary TB that most frequently appeared in this study sample were weight loss (85.3%) followed by shortness of breath (20.6%), night sweats (8.8%) and coughing up blood (8.8%). This is in accordance with previous research in Africa which showed that symptoms of weight loss were quite common, experienced by 80% of the study sample. However, other complaints such as coughing, fever and night sweats were also experienced by more than 50% of the sample (Brennan et al., 2020)

Meanwhile, this study only showed symptoms of weight loss that appeared in more than 50% of the sample. Weight loss in HIV - Pulmonary TB co-infection is multifactorial, involving increased metabolic needs, malabsorption, loss of appetite, catabolic processes, opportunistic infections, impaired immune function, medication side effects, and psychosocial factors. Early detection and management of weight loss are

important aspects of comprehensive care provided to people co-infected with HIV and pulmonary TB (Brennan et al., 2020) (Nyoko, Putra, & Sawitri, 2014)

The radiological features that were frequently seen in patients coinfected with HIV–pulmonary TB in this study were infiltrates (35.3%), followed by fibrosis and pleural effusion (29.4% each), and cavities (11.8%). The dominance of infiltrate images on radiology in this study is like the latest research in 2023 by Takhar et al. in India, which in its research found that 27.4% of its research samples showed a picture of consolidation or infiltrate (Takhar et al., 2023)

The radiological appearance of TB patients depends on the severity of the HIV infection experienced. In the early stages, radiological images can still appear typical, such as infiltrates, cavity fibrosis and calcification at the apex. However, when immunity begins to decline in advanced stages of HIV, the radiological picture becomes atypical with consolidation or infiltrates in the inferior part of the lungs or enlargement of the hilar glands. Miliary tuberculosis, which is characterized by widespread spread of Mycobacterium tuberculosis throughout the body, is also more common in people with HIV. Radiologically, miliary TB appears in the form of many small nodules scattered throughout the lung fields. This pattern is associated with hematogenous spread of infection (Nyoko et al., 2014)

Relationship between MMP-1 Levels and Clinical Symptoms in HIV - Pulmonary TB Coinfection

This study proves an independent relationship between MMP-1 levels and clinical symptoms in patients coinfected with HIV-TB. The results of Fisher exact analysis showed a significant relationship between MMP-1 levels and clinical symptoms ($p<0.05$). Additionally, multivariate analysis showed that only MMP-1 levels were significantly associated with clinical symptoms ($p<0.05$).

These results are in accordance with previous studies reporting that HIV infection causes dysregulation of MMP activity which will influence disease development (Ju et al., 2009). This study is supported by previous studies regarding differences in MMP-1 levels in 14 non-TB HIV patients and 20 pulmonary HIV-TB patients. This research shows that there are significant differences ($p<0.01$) MMP-1 levels in non-TB HIV patients compared with HIV-TB patients, where MMP-1 levels were found to be 5.7 times higher in pulmonary HIV-TB patients (Elkington et al., 2011)

The severity of TB infection in HIV patients may be influenced by MMP levels, reflecting the complex interaction between these two conditions. MMP-1, a matrix metalloproteinase, has been implicated in tissue destruction and is upregulated during TB infection (Walker et al., 2012)

Hypoxic conditions in TB have been shown to increase the expression and secretion of the MMP-1 gene during Mtb infection, thus showing the relevance of MMP-1 in TB pathogenesis (Belton et al., 2016). Additionally, MMP levels have been associated with the severity and extent of disease in TB, reflecting the potential impact of MMP dysregulation on the development of TB symptoms (Kumar et al., 2018)

Furthermore, the severity of TB infection in HIV patients can be influenced by immunological disorders caused by HIV/AIDS. This increases the proliferation of M. tuberculosis and the severity of TB disease. In addition, TB/HIV coinfection is associated with a high risk of loss-to-follow-up, death, and high HIV RNA levels (Resende et al., 2023). Treatment failure has also been reported to be significantly worse among HIV patients with TB co-infection compared to the TB-only population (Olowe, Makanjuola, Adekanmi, Adefioye, & Olowe, 2017)

In this study, there was a significant difference in MMP-1 levels with clinical symptoms compared to those without clinical symptoms. Another study in 2017 examined the concentrations of various MMPs and cytokines in HIV patients with TB with CD4 counts <200 compared to HIV negative patients to determine the mediators that drive pathological immunity from Mtb. This study also showed a significant difference in MMP-1 levels in TB patients with HIV, which was 1,213 pg/mg, while in controls it was 129 pg/mg (Walker et al., 2017). In further research, the same researchers found consistent results, namely that HIV patients with confirmed TB infection had higher MMP-1 levels than those without TB infection with median values of 5,316 and 4,477 pg/mg respectively (Walker et al., 2023). In addition, HIV-TB co-infected patients were found to have a higher risk of experiencing poor treatment outcomes compared to patients who were only infected with TB (Hayibor et al., 2020).

MMP-1 levels are also known to have a correlation with the severity of TB infection. A 2013 study showed several MMP and TIMP concentrations were increased in TB patients at the time of presentation with clinical symptoms, and that MMP-1 correlated most closely with TB severity. As the patient's clinical improvement, MMP1 concentrations decreased rapidly during treatment. The study concluded that MMPs, especially MMP-1 and MMP-1 activators, were increased in TB patients and were associated with clinical symptoms. MMP-1 concentrations decreased sharply with treatment and increased with higher TB severity scores high (Ugarte-Gil, et al 2013).

## Relationship between MMP-1 Levels and Radiological Features in Pulmonary HIV-TB Coinfection

The results of this research study found a relationship between MMP-1 levels and radiological images in patients coinfected with HIV-TB. The results of Fisher exact analysis showed a significant relationship between MMP-1 levels and radiological images ($p<0.05$). Additionally, multivariate analysis showed that only MMP-1 levels were significantly associated with radiological images ($p<0.05$).

Matrix metalloproteinase is an endopeptidase with the ability to degrade extracellular matrix components. Cavity formation is very important in the pathogenesis of Mtb, because it promotes the transmission of TB infection. The cavity in the lung is a place that is immune to immunity with a high bacterial load, and cannot be penetrated by antimycobacterial drugs, which causes a higher risk of treatment failure and recurrence of TB infection (Dheda, et al. 2018).

MMPs have been implicated in the pathology of lung tissue damage and cavitation, because collectively, MMPs can degrade all components of the fibrillary extracellular matrix. Significantly increased MMP gene expression was found in human respiratory cells (alveolar macrophages, bronchial epithelial cells, and fibroblasts) and macrophages in response to Mtb infection and/or stimulation by conditioned medium from Mtb-infected monocytes (CoMtb), resulting in increased MMP secretion (Ong, Elkington, & Friedland, 2014). Overall, MMPs have a complex role in the immunopathology of pulmonary HIV-TB co-infection (Walker et al., 2012)

In the lung, MMP-1 (known as interstitial collagenase) plays an important role in degrading the primary collagen architecture in the tissue parenchyma. Physiologically, MMPs are generally not expressed in healthy tissue, where their expression is only seen in tissue that is inflamed, or that is undergoing remodeling. Epithelial cells in the lung are a significant source of MMPs because they express one of them, namely MMP1. In TB, over-expression and secretion, especially of MMP-1, is associated with progression from consolidation areas to cavities with high bacterial loads. Interestingly, MMP-1 has been shown to be regulated by mitogen activated protein kinase (MAPK) signaling in Mtb-infected macrophages (Amaral et al., 2021)

Intracellular signaling involving p38 and the extracellular signal-regulated protein kinase (ERK) mitogen-activated protein kinase (MAPK) pathway is important for regulation. MMPs in macrophages in response to Mtb infection. An increase in the MMP-1 enzyme has been shown to cause significant damage to the alveolar walls and lung parenchyma, through enzymatic degradation of collagen (Rohlwink et al., 2019)

This study found a significant relationship between MMP-1 levels and the incidence of radiological images in HIV-TB co-infection. The theory states that disruption of ECM balance is the starting point in the pathogenesis of lung cavitation. Cavity formation must involve the action of proteases, especially MMPs capable of degrading lung structural fibrils, such as MMP-1 (Elkington et al., 2011). Varying MMP activity has been demonstrated in HIV-1-infected and HIV-1-uninfected TB individuals. Research by Walker, et al. in 2017 showed conflicting results with this study. This study shows that HIV-1 infection in TB patients causes a decrease in lung MMP concentrations and a reduction in cavitary lesions on radiological images of the lungs, leading to the conclusion that patients who have HIV-TB co-infection may have less lung matrix damage than patients who have TB alone (Walker et al., 2017). Meanwhile, research by Lou, et al. have shown that Mtb infection increases the expression of MMP-1, MMP-9, and miR-223, while inhibiting the expression of BMAL1 (Lou, Wang, Zhang, & Qiu, 2017)

Additionally, mycobacterial lipoarabinomannan, a major antigenic cell wall component, has been found to increase MMP-1 mRNA accumulation in broncho-alveolar lavage fluid cells isolated from active pulmonary TB patients (Elkington et al., 2005). In addition, Mtb was shown to induce MMP-1 and MMP-10 in peripheral blood mononuclear cells (Coussens et al., 2009). Another study supporting these results presents evidence that MMP-1, which can specifically degrade type I collagen, promotes lung

tissue destruction in TB. The study also found MMP-1 levels were significantly increased in the patients TB while TIMPs levels decrease. In addition, MMP-1 levels in HIV-TB pulmonary patients with extensive radiological features were 8.5 times significantly higher than those with minor radiological features (p=0.030) (Elkington et al., 2011)

Further research is needed to fully understand its regulation and specific functions in this context. Thus, targeting MMP activity is a potential therapeutic approach to control TB by inhibiting matrix destruction and reducing TB-related morbidity and mortality, especially in patients with HIV-TB co-infection.

## Research Limitations

This study has several limitations, including not having specifically analyzed the radiological images in the research sample in the category of lung lesion location such as the lobe involved, the area of the lesion can help in assessing the Patho mechanism pattern of MMP-1, but this is a little difficult to do due to the lack of variety in the sample population. In addition, the samples in this study had received ARV treatment, so there is a possibility that MMP-1 levels in this study were influenced by treatment with ARVs. This research can be developed in the future by using research designs that have a higher level of evidence, such as cohort tests to clinical trials

## Conclusion

MMP-1 levels are related to the clinical picture of HIV-TB pulmonary co-infected patients. MMP-1 levels have a relationship with the radiological appearance of HIV-pulmonary TB co-infected patients

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