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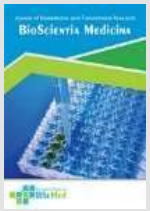

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Procalcitonin Levels in Pulmonary Tuberculosis and Bacterial Pneumonia: A Cross-Sectional Study at a Tertiary Hospital in Indonesia

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A B S T R A C T

Background: Pulmonary tuberculosis (TB) and bacterial pneumonia are respiratory infections with high morbidity and mortality rates. Despite having similar clinical symptoms and radiological findings, these conditions require different treatment approaches. Procalcitonin is a potential biomarker to differentiate these conditions, as its levels tend to increase in bacterial infections but not in TB. This study aims to compare procalcitonin levels in patients with pulmonary TB and bacterial pneumonia. **Methods:** This research employed an observational analytic design with a cross-sectional approach conducted at Dr. Mohammad Hoesin General Hospital (RSMH), Palembang. The study subjects were patients with pulmonary TB and bacterial pneumonia who met the inclusion and exclusion criteria. Procalcitonin levels were measured using ELISA methods. Data were analyzed to determine differences in procalcitonin levels between the two groups. **Results:** The study found that procalcitonin levels in bacterial pneumonia patients were significantly higher than those in pulmonary TB patients ($p<0.05$). These findings indicate that procalcitonin levels can serve as a diagnostic parameter to distinguish between the two conditions. **Conclusion:** Procalcitonin levels can be a useful biomarker for differentiating pulmonary TB from bacterial pneumonia. This biomarker is expected to assist clinicians in making more accurate diagnoses and expediting clinical decision-making.

1. Introduction

Respiratory infections remain a leading cause of morbidity and mortality worldwide, posing a significant challenge to public health. Among these infections, pulmonary tuberculosis (TB) and bacterial pneumonia stand out as two of the most prevalent and serious conditions, particularly in low- and middle-income countries. These diseases, while distinct in their etiology and pathogenesis, often present with overlapping clinical and radiological features, making accurate and timely diagnosis a critical challenge. TB, caused by the bacterium Mycobacterium tuberculosis, has plagued humanity for centuries, and despite significant advances in treatment and prevention strategies, it continues to be a major global health concern. The World Health Organization (WHO) estimates that in 2022, there were 10.6 million new TB cases worldwide, leading to 1.6 million deaths. The global TB epidemic is further complicated by the emergence of drug-resistant strains, making treatment more challenging and highlighting the need for new diagnostic and therapeutic approaches. Bacterial pneumonia, an acute infection of the lung parenchyma, is another major contributor to the global burden of respiratory diseases. Streptococcus pneumoniae is the most common causative agent,

followed by other bacteria such as *Haemophilus influenzae, Klebsiella pneumoniae,* and *Staphylococcus aureus*. While bacterial pneumonia can affect individuals of all ages, it poses a particularly serious threat to the elderly, young children, and those with underlying health conditions. The clinical presentation of bacterial pneumonia can range from mild to severe, and in some cases, it can lead to life-threatening complications such as sepsis and respiratory failure.[1-3]

The accurate and prompt differentiation between TB and bacterial pneumonia is essential for guiding appropriate treatment decisions and improving patient outcomes. However, this can be a significant challenge in clinical practice due to the considerable overlap in their clinical and radiological manifestations. Both conditions can present with symptoms such as cough, fever, chest pain, and shortness of breath, and chest radiographs may reveal similar findings such as infiltrates and consolidation. Traditional diagnostic methods, such as sputum smear microscopy and culture for TB, and blood or sputum cultures for bacterial pneumonia, often have limitations. Sputum smear microscopy has low sensitivity, particularly in patients with HIV co-infection or paucibacillary TB, while culture can take several weeks to yield results. Blood and sputum cultures for bacterial pneumonia can also be time-consuming and may not always identify the causative organism. The limitations of traditional diagnostic methods and the significant overlap in the clinical presentation of TB and bacterial pneumonia underscore the urgent need for novel diagnostic tools that can rapidly and accurately differentiate between these two conditions. Biomarkers, measurable biological indicators of a disease state, have emerged as promising candidates for improving the diagnosis and management of respiratory infections. Procalcitonin, a prohormone of calcitonin, has attracted considerable attention as a potential biomarker for differentiating bacterial from non-bacterial infections. Under normal physiological conditions, procalcitonin levels in the blood are very low. However, in response to bacterial infections, procalcitonin levels rise rapidly and significantly, making it a potentially useful marker for guiding clinical decision-making.[4-7]

Several studies have investigated the role of procalcitonin in differentiating TB from bacterial pneumonia, with promising results. These studies have generally found that procalcitonin levels are significantly higher in patients with bacterial pneumonia compared to those with TB. This differential expression of procalcitonin is thought to be related to the distinct inflammatory responses elicited by these two conditions. In bacterial pneumonia, the host immune response is typically characterized by a robust pro-inflammatory reaction, leading to the release of cytokines and other mediators that stimulate the production of procalcitonin. In contrast, the inflammatory response in TB is often less pronounced and more localized, resulting in lower levels of procalcitonin. Despite the growing body of evidence supporting the role of procalcitonin in differentiating TB from bacterial pneumonia, there is still limited data on its use in this context, particularly in Indonesia, a country with a high burden of both diseases.[8-10] Therefore, this study aimed to compare procalcitonin levels in patients with pulmonary TB and bacterial pneumonia at a tertiary hospital in Indonesia.

2. Methods

This study employed a cross-sectional, observational design to investigate the levels of procalcitonin in patients with pulmonary tuberculosis (TB) and bacterial pneumonia. The research was conducted at Dr. Mohammad Hoesin General Hospital (RSMH), a tertiary referral hospital located in Palembang, Indonesia. As a tertiary referral hospital, RSMH receives patients with a wide range of medical conditions, including complex and severe cases, from both primary and secondary care facilities. This selection ensured that the study population would include a diverse range of patients with TB and bacterial pneumonia, enhancing the generalizability of

the findings. The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Universitas Sriwijaya.

The study population consisted of adult patients (18 years or older) admitted to RSMH with a confirmed diagnosis of either pulmonary TB or bacterial pneumonia. The diagnosis of pulmonary TB was established based on the presence of clinical symptoms suggestive of TB, such as cough, fever, weight loss, and night sweats, along with radiological findings consistent with TB, and positive sputum smear microscopy or culture for M. tuberculosis. The diagnosis of bacterial pneumonia was based on the presence of clinical symptoms suggestive of pneumonia, such as cough, fever, chills, and shortness of breath, along with radiological findings consistent with pneumonia, and positive blood or sputum cultures for bacterial pathogens. To ensure the integrity of the study and minimize the potential for confounding factors, strict inclusion and exclusion criteria were applied. Patients were included in the study if they had a confirmed diagnosis of either pulmonary TB or bacterial pneumonia based on clinical, radiological, and laboratory findings. Patients were excluded from the study if they had any other known causes of elevated procalcitonin levels, such as sepsis, severe trauma, or surgery. These criteria were implemented to ensure that the study population was as homogeneous as possible, minimizing the risk of confounding factors influencing the results. The sample size for this study was calculated using the following formula;

$$n = 2 * (Z\alpha/2 + Z\beta)^2 * (\sigma1^2 + \sigma2^2) / (\mu1 - \mu2)^2$$

Notes:

n = the required sample size per group;

$Z\alpha/2$ = the critical value of the standard normal distribution at $\alpha/2$ (for a 95% confidence level, $Z\alpha/2$ = 1.96);

$Z\beta$ = the critical value of the standard normal distribution at β (for a power of 80%, $Z\beta$ = 0.84);

$\sigma1$ and $\sigma2$ = the standard deviations of procalcitonin levels in the TB and pneumonia groups, respectively;

$\mu1$ and $\mu2$ = the mean procalcitonin levels in the TB and pneumonia groups, respectively.

Based on previous studies, the mean procalcitonin levels in the TB and pneumonia groups were estimated to be 0.5 ng/mL and 5 ng/mL, respectively, with a standard deviation of 2 ng/mL in both groups. Using these values, the calculated sample size was 29 per group. To account for potential dropouts, a total of 30 patients per group were enrolled in the study.

After obtaining written informed consent from each participant, demographic and clinical data were collected from their medical records. The data collected included age, gender, nutritional status, presence of comorbidities (such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), and chronic kidney disease), smoking status, alcohol consumption, and HIV status. Nutritional status was assessed using the body mass index (BMI), with patients classified as malnourished if their BMI was below 18.5 kg/m^2. Smoking status was categorized as smoker or non-smoker, and alcohol consumption was categorized as yes or no. HIV status was determined based on serological testing. In addition to demographic and clinical data, blood samples were collected from each participant for the measurement of procalcitonin levels. The blood samples were collected by venipuncture into sterile tubes containing ethylenediaminetetraacetic acid (EDTA) as an anticoagulant. The samples were then centrifuged to separate the plasma, which was stored at -80°C until analysis.

Procalcitonin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. The ELISA technique is a widely used method for detecting and quantifying specific proteins in biological samples. It is based on the principle of antibody-antigen recognition, where an antibody specific to the protein of interest is used to capture the protein from the sample. A secondary antibody, conjugated to an enzyme, is then added to bind to the captured protein. The enzyme catalyzes a reaction that produces a measurable signal, which is proportional to the concentration of the protein in the sample. In this

study, the ELISA kit used for procalcitonin measurement was the Elecsys BRAHMS PCT assay (Roche Diagnostics, Mannheim, Germany). This assay is a highly sensitive and specific method for measuring procalcitonin levels in human serum and plasma. The assay was performed according to the manufacturer's instructions. Briefly, 20 µL of plasma was added to the wells of a microtiter plate coated with a monoclonal antibody specific for procalcitonin. After incubation, the wells were washed, and a second monoclonal antibody, conjugated to ruthenium, was added. Following another incubation and washing step, the wells were read in an Elecsys 2010 analyzer (Roche Diagnostics). The analyzer measures the electrochemiluminescence signal generated by the ruthenium label, which is proportional to the concentration of procalcitonin in the sample. The results were expressed in nanograms per milliliter (ng/mL).

Data were analyzed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on the distribution of the data. Categorical variables were expressed as frequencies and percentages. The Mann-Whitney U test was used to compare procalcitonin levels between the two groups. The Mann-Whitney U test is a nonparametric test that is used to compare the distributions of two independent groups. It is appropriate for data that are not normally distributed or when the sample size is small. A p-value of less than 0.05 was considered statistically significant. The p-value is the probability of obtaining the observed results, or more extreme results if there is no difference between the two groups. A p-value of less than 0.05 indicates that the observed difference is unlikely to be due to chance and is therefore considered statistically significant.

3. Results

Table 1 presents the demographic and clinical characteristics of the 60 participants enrolled in the study, divided into two groups: the TB group (n=30) and the Pneumonia group (n=30). Both groups showed a similar distribution in terms of age and gender, with no statistically significant differences. This suggests that these factors are unlikely to confound the comparison of procalcitonin levels between the two groups. A noteworthy difference was observed in nutritional status, with a significantly higher proportion of malnourished individuals in the TB group (43.3%) compared to the Pneumonia group (30.0%). This finding aligns with the known association between TB and malnutrition, reflecting the chronic nature of TB and its potential impact on nutritional status. The prevalence of comorbidities, including diabetes mellitus, hypertension, COPD, and chronic kidney disease, was comparable between the two groups, with no statistically significant differences. This indicates that the presence of these comorbidities is unlikely to be a major confounding factor in the analysis of procalcitonin levels. Similarly, no significant differences were found between the groups regarding smoking status and alcohol consumption. This further supports the comparability of the two groups in terms of these lifestyle factors. The majority of participants in both groups were HIV-negative, with no significant difference in the prevalence of HIV infection between the groups. This minimizes the potential confounding effect of HIV infection on procalcitonin levels. A highly significant difference was observed in symptom duration, with the TB group experiencing symptoms for a considerably longer period (median 21 days) compared to the Pneumonia group (median 5 days). This difference is consistent with the typical clinical course of these diseases, where TB often presents with a more insidious onset and prolonged duration of symptoms compared to the relatively acute presentation of bacterial pneumonia.

Table 1. Participant characteristics.

Characteristic	TB group (n=30)	Pneumonia group (n=30)	p-value
Age (years)			0.787
<60	19 (63.3%)	20 (66.7%)	
≥60	11 (36.7%)	10 (33.3%)	
Gender			0.791
Male	19 (63.3%)	18 (60.0%)	
Female	11 (36.7%)	12 (40.0%)	
Nutritional status			0.037
Malnourished	13 (43.3%)	9 (30.0%)	
Not malnourished	17 (56.7%)	21 (70.0%)	
Comorbidities			
Diabetes mellitus	5 (16.7%)	7 (23.3%)	0.519
Hypertension	9 (30.0%)	12 (40.0%)	0.417
COPD	2 (6.7%)	4 (13.3%)	0.389
Chronic kidney disease	3 (10.0%)	6 (20.0%)	0.278
Smoking status			0.812
Smoker	12 (40.0%)	11 (36.7%)	
Non-smoker	18 (60.0%)	19 (63.3%)	
Alcohol consumption			0.543
Yes	8 (26.7%)	6 (20.0%)	
No	22 (73.3%)	24 (80.0%)	
HIV status			0.371
Positive	2 (6.7%)	1 (3.3%)	
Negative	28 (93.3%)	29 (96.7%)	
Symptom duration (days)			<0.001
TB group	Median: 21 (range: 7-60)		
Pneumonia group		Median: 5 (range: 2-14)	

Table 2 provides a detailed comparison of procalcitonin levels between the Pulmonary TB group and the Bacterial Pneumonia group, further stratified by various demographic and clinical factors. The most striking observation is the stark difference in procalcitonin levels between the two groups. The Pneumonia group exhibited significantly higher procalcitonin levels compared to the TB group, as evidenced by the median (IQR), mean ± SD, and range values. This finding strongly supports the hypothesis that procalcitonin can effectively differentiate between bacterial and non-bacterial respiratory infections. The substantially elevated procalcitonin levels in the Pneumonia group are consistent with the robust inflammatory response triggered by bacterial infections, leading to a surge in procalcitonin production. In contrast, the lower levels observed in the TB group reflect the more contained and less intense inflammatory response characteristic of TB. When stratified by age and gender, no significant differences in procalcitonin levels were observed within each group. This suggests that age and gender do not significantly influence procalcitonin levels in either TB or bacterial pneumonia. This finding further strengthens the potential of procalcitonin as a reliable biomarker, as its diagnostic utility appears to be

independent of these demographic factors. Although the Pneumonia group generally showed higher procalcitonin levels, the difference was not statistically significant when stratified by nutritional status. This implies that malnutrition, a common finding in TB patients, does not appear to substantially affect procalcitonin levels. This observation is important as it suggests that procalcitonin can be a useful marker even in malnourished individuals, a population often at higher risk for both TB and pneumonia. Similarly, the presence of comorbidities such as diabetes mellitus, hypertension, COPD, and chronic kidney disease did not significantly alter procalcitonin levels within each group. This finding further supports the robustness of procalcitonin as a diagnostic marker, indicating that its levels are not significantly influenced by the presence of these common comorbidities.

Table 2. Procalcitonin levels in participants with pulmonary TB and bacterial pneumonia.

Variable	TB Group (n=30)	Pneumonia Group (n=30)	p-value
Procalcitonin (ng/mL)			
Median (IQR)	0.33 (0.12-1.00)	4.70 (0.80-37.10)	<0.001
Mean ± SD	0.45 ± 0.28	8.55 ± 9.32	
Range	0.12 - 1.00	0.80 - 37.10	
Procalcitonin by age			
<60 years			0.704
Median (IQR)	0.85 (0.14-18.71)	1.00 (0.12-18.11)	
≥60 years			
Median (IQR)	0.85 (0.14-18.71)	1.00 (0.12-18.11)	
Procalcitonin by gender			
Male			0.659
Median (IQR)	0.85 (0.14-37.10)	0.95 (0.12-22.24)	
Female			
Median (IQR)	0.85 (0.14-37.10)	0.95 (0.12-22.24)	
Procalcitonin by nutritional status			
Malnourished			0.179
Median (IQR)	0.51 (0.12-14.73)	1.32 (0.15-18.71)	
Not malnourished			
Median (IQR)	0.51 (0.12-14.73)	1.32 (0.15-18.71)	
Procalcitonin by comorbidity			
Diabetes mellitus			0.380
Median (IQR)	3.05 (0.15-9.50)	0.75 (0.12-37.10)	
No diabetes mellitus			
Median (IQR)	3.05 (0.15-9.50)	0.75 (0.12-37.10)	
Hypertension			0.890
Median (IQR)	0.83 (0.14-22.24)	0.98 (0.12-37.10)	
No hypertension			
Median (IQR)	0.83 (0.14-22.24)	0.98 (0.12-37.10)	
COPD			0.727
Median (IQR)	2.42 (0.22-8.90)	0.88 (0.12-37.10)	
No COPD			
Median (IQR)	2.42 (0.22-8.90)	0.88 (0.12-37.10)	
Chronic kidney disease			0.437
Median (IQR)	1.18 (0.18-14.73)	0.85 (0.12-37.10)	
No chronic kidney disease			
Median (IQR)	1.18 (0.18-14.73)	0.85 (0.12-37.10)	

Table 3 presents the diagnostic accuracy of procalcitonin in differentiating pulmonary TB from bacterial pneumonia, using a cut-off value of 0.9 ng/mL. This table highlights the potential of procalcitonin as a valuable tool for distinguishing between these two conditions. With a sensitivity and

specificity of 93.3%, procalcitonin demonstrates excellent accuracy in correctly identifying individuals with TB and pneumonia. This means that the test correctly identifies 93.3% of patients with pneumonia (true positive rate) and 93.3% of patients with TB (true negative rate). The high sensitivity indicates a low rate of false negatives (misclassifying pneumonia as TB), while the high specificity indicates a low rate of false positives (misclassifying TB as pneumonia). These findings are crucial as misdiagnosis can lead to inappropriate treatment and adverse outcomes. The area under the ROC curve (AUC) of 0.99 signifies that procalcitonin has outstanding discriminatory power. An AUC of 1 represents a perfect test, and a value of 0.99 suggests that procalcitonin is highly effective in differentiating between TB and pneumonia. The odds ratio (OR) of 196 indicates a very strong association between elevated procalcitonin levels and the presence of bacterial pneumonia. This means that individuals with pneumonia are 196 times more likely to have elevated procalcitonin levels compared to those with TB. This further emphasizes the potential of procalcitonin as a diagnostic marker.

Table 3. Diagnostic accuracy and odds ratio of procalcitonin for differentiating pulmonary TB from bacterial pneumonia.

Variable	Value	95% CI	p-value
Cut-off Value (ng/mL)	0.9	-	<0.001
Sensitivity (%)	93.3	78.5 - 98.8	
Specificity (%)	93.3	78.5 - 98.8	
Area Under the ROC Curve (AUC)	0.99	0.98 - 1.00	
Odds Ratio (OR)	196	45.3 - 852.1	<0.001

4. Discussion

This study unequivocally demonstrates the potential of procalcitonin as a valuable biomarker for differentiating between pulmonary tuberculosis (TB) and bacterial pneumonia. The significantly elevated procalcitonin levels observed in patients with bacterial pneumonia compared to those with pulmonary TB align with a growing body of research and underscore the potential of this biomarker to revolutionize the accurate and timely diagnosis of these two respiratory conditions. The ability to rapidly and accurately differentiate between TB and bacterial pneumonia is not merely an academic exercise it holds paramount importance in clinical practice. Misdiagnosis can have dire consequences, leading to inappropriate treatment, delayed initiation of correct therapy, and potentially resulting in increased morbidity and mortality. Traditional diagnostic methods, such as sputum smear microscopy and chest radiography, while valuable, often lack the sensitivity and specificity to reliably distinguish between these two conditions, especially in the early stages of disease or in resource-limited settings. The results of this study suggest that procalcitonin can effectively bridge this diagnostic gap and contribute to significantly improved patient outcomes. The stark contrast in procalcitonin levels observed between the two study groups highlights the distinct pathophysiological mechanisms underlying these infections. Bacterial pneumonia, typically caused by pathogens like *Streptococcus pneumoniae* and *Haemophilus influenzae*, triggers a rapid and intense inflammatory response. This response is characterized by the activation of innate immune cells, such as neutrophils and macrophages, which release a cascade of pro-inflammatory cytokines, including IL-6 and TNF-α. These cytokines, in turn, stimulate the production of procalcitonin, primarily from neuroendocrine cells throughout the body, leading to a surge in serum levels. In contrast, TB, caused by *Mycobacterium tuberculosis*, follows a more insidious course. The mycobacteria possess unique strategies to evade the host immune system, allowing them to persist within macrophages and establish a chronic infection. This

intracellular survival leads to a more contained and granulomatous inflammatory response, with a less pronounced systemic cytokine release. Consequently, the stimulation of procalcitonin production is muted, resulting in significantly lower levels compared to bacterial pneumonia. Procalcitonin possesses several advantages over other biomarkers and diagnostic tools currently used in the evaluation of respiratory infections. Firstly, its rapid kinetics make it an ideal marker for acute settings. Procalcitonin levels rise within hours of the onset of bacterial infection, peaking within 24-48 hours, and decline with successful treatment. This rapid response allows for prompt diagnosis and timely initiation of appropriate therapy. Secondly, procalcitonin demonstrates superior specificity compared to other inflammatory markers, such as C-reactive protein (CRP). CRP, while widely used, is a non-specific marker of inflammation and can be elevated in various conditions, including both bacterial and viral infections, as well as in non-infectious inflammatory states. This lack of specificity can lead to diagnostic uncertainty and potentially inappropriate antibiotic use. Procalcitonin, on the other hand, exhibits a more targeted response to bacterial infections, making it a more reliable indicator of bacterial etiology. Furthermore, procalcitonin's ability to differentiate between bacterial and non-bacterial infections can be particularly valuable in guiding antibiotic stewardship. The indiscriminate use of antibiotics has fueled the rise of antibiotic resistance, posing a significant threat to global health. Procalcitonin can aid in identifying patients who are truly likely to benefit from antibiotics, thereby promoting judicious antibiotic use and preserving the effectiveness of these life-saving drugs. The results of this study have profound implications for improving patient outcomes in the management of respiratory infections. In patients presenting with symptoms suggestive of either TB or bacterial pneumonia, the measurement of procalcitonin levels can provide crucial information to guide clinical decision-making. A high procalcitonin level, exceeding a predetermined threshold, would strongly suggest a bacterial etiology, prompting the initiation of empiric antibiotic therapy. Conversely, a low procalcitonin level would favor a diagnosis of TB, leading to further investigations, such as sputum culture, molecular testing, and the prompt initiation of anti-TB treatment. By facilitating accurate and timely diagnosis, procalcitonin can help to avoid the pitfalls of misdiagnosis and inappropriate treatment. In the case of TB, delayed diagnosis and treatment can lead to disease progression, transmission to others, and the development of drug resistance. In bacterial pneumonia, delayed antibiotic therapy can result in complications such as sepsis, respiratory failure, and even death. Procalcitonin can help to mitigate these risks by enabling prompt and targeted treatment. The potential benefits of procalcitonin are particularly significant in resource-limited settings, where access to advanced diagnostic tests, such as culture or molecular assays, may be limited. In these settings, healthcare providers often rely on clinical judgment and basic investigations, such as chest radiography and sputum smear microscopy, which may not always be conclusive. Procalcitonin, with its high sensitivity and specificity, can serve as a valuable adjunct to these traditional methods, aiding in more accurate diagnosis and improving patient management. Moreover, the use of procalcitonin can contribute to cost-effective healthcare delivery in resource-constrained environments. By reducing the need for extensive and often expensive diagnostic testing, procalcitonin can help to optimize resource allocation and improve healthcare efficiency.[11-13]

The striking difference in procalcitonin levels observed between the bacterial pneumonia and pulmonary tuberculosis (TB) groups in this study underscores the intricate interplay between the host immune system and these distinct pathogens. The significantly elevated procalcitonin levels in bacterial pneumonia are not merely a coincidental finding, they reflect a complex cascade of immunological events triggered by the invading bacteria. This intricate dance between host and pathogen ultimately determines the magnitude of the inflammatory response and the

subsequent production of procalcitonin. Bacterial pneumonia, typically caused by pathogens like *Streptococcus pneumoniae* and *Haemophilus influenzae*, elicits a rapid and robust inflammatory response. This response is orchestrated by a diverse array of immune cells, including neutrophils, macrophages, and dendritic cells, which act in concert to combat the invading bacteria. The initial encounter between the host and the bacteria triggers the activation of pattern recognition receptors (PRRs) in immune cells. These PRRs recognize conserved molecular patterns in the bacteria, known as pathogen-associated molecular patterns (PAMPs). The recognition of PAMPs by PRRs sets off a signaling cascade that culminates in the production of pro-inflammatory cytokines, chemokines, and other mediators. Among the key cytokines involved in this inflammatory response are interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). IL-6 is a pleiotropic cytokine that plays a central role in orchestrating the acute-phase response, a systemic reaction to infection or injury. TNF-α, another potent pro-inflammatory cytokine, contributes to the recruitment of immune cells to the site of infection and the activation of antimicrobial mechanisms. These pro-inflammatory cytokines, along with other mediators, act as powerful stimuli for the production of procalcitonin. While procalcitonin is primarily produced by the C-cells of the thyroid gland under normal physiological conditions, during bacterial infection, its production is dramatically upregulated in various cell types throughout the body, including monocytes, macrophages, and neuroendocrine cells. This widespread production of procalcitonin contributes to the rapid and significant increase in its serum levels observed in bacterial pneumonia. In contrast to the acute and intense inflammatory response seen in bacterial pneumonia, the immune response to Mycobacterium tuberculosis, the causative agent of TB, is more subtle and protracted. This difference is largely attributed to the unique ability of M. tuberculosis to evade the host immune system and establish a persistent infection. M. tuberculosis has evolved sophisticated strategies to survive and replicate within macrophages, the very immune cells that are tasked with eliminating it. The mycobacteria are able to manipulate the intracellular environment of macrophages, preventing the fusion of phagosomes with lysosomes, a crucial step in the killing of intracellular pathogens. This intracellular persistence allows M. tuberculosis to evade the full brunt of the host immune response and establish a chronic infection. The immune response to TB is characterized by the formation of granulomas, organized aggregates of immune cells that attempt to contain the infection. While granulomas serve to limit the spread of M. tuberculosis, they also contribute to the chronic nature of the disease. The inflammatory response within granulomas is tightly regulated, with a balance between pro-inflammatory and anti-inflammatory signals. This controlled inflammatory environment, while essential for containing the infection, also results in a less pronounced systemic cytokine release and a lower overall inflammatory response compared to bacterial pneumonia. Consequently, the stimulation of procalcitonin production in TB is muted, leading to significantly lower levels compared to bacterial pneumonia. This difference in procalcitonin levels reflects the distinct immunological strategies employed by the host to combat these two pathogens. The contrasting procalcitonin levels observed in bacterial pneumonia and TB highlight the dynamic interplay between the host immune system and the invading pathogen. The magnitude of the inflammatory response, the types of cytokines released, and the ultimate production of procalcitonin are all influenced by the specific pathogen and its interaction with the host. In bacterial pneumonia, the rapid and intense inflammatory response, characterized by a surge in pro-inflammatory cytokines, drives the significant elevation of procalcitonin levels. This elevation serves as a marker of the severity of the infection and can guide clinical decision-making regarding antibiotic therapy. In TB, the more contained and granulomatous inflammatory response, with its lower

cytokine production, results in lower procalcitonin levels. This finding can help to differentiate TB from bacterial pneumonia and guide the appropriate diagnostic and therapeutic interventions. The findings of this study underscore the potential of procalcitonin not only as a diagnostic biomarker but also as a tool to gain deeper insights into the complex immunological interactions underlying infectious diseases. By studying the dynamics of procalcitonin production in different infections, researchers can gain a better understanding of the host immune response and identify potential targets for therapeutic intervention. Furthermore, procalcitonin's ability to reflect the severity of bacterial infection can aid in risk stratification and prognostication. Higher procalcitonin levels have been associated with more severe disease and worse outcomes in various bacterial infections, including pneumonia. This information can help clinicians to identify patients at higher risk of complications and tailor their management accordingly.[14-16]

The results of this study have important clinical implications for the diagnosis and management of patients with suspected TB or bacterial pneumonia. In patients presenting with respiratory symptoms and radiological findings suggestive of either condition, the measurement of procalcitonin levels can provide valuable information to guide clinical decision-making. A procalcitonin level above a certain threshold could suggest a bacterial infection, prompting the initiation of antibiotic therapy. Conversely, a low procalcitonin level could suggest TB, leading to further investigations, such as sputum culture and molecular testing, and the initiation of anti-TB treatment. The use of procalcitonin as a diagnostic marker could also help to reduce the unnecessary use of antibiotics, which is a major driver of antibiotic resistance. By accurately identifying patients with bacterial infections, procalcitonin could help to ensure that antibiotics are used only when necessary, preserving their effectiveness for future generations. Procalcitonin has several characteristics that make it an ideal diagnostic tool in the clinical setting. It has a rapid response time, with levels rising within hours of the onset of bacterial infection. It is also highly specific for bacterial infections, meaning that it is not elevated in viral or fungal infections. Additionally, procalcitonin levels correlate with the severity of infection, making it a useful prognostic marker. In patients with suspected TB or bacterial pneumonia, procalcitonin can be used as an adjunctive diagnostic test to help differentiate between the two conditions. A procalcitonin level above a certain threshold, which may vary depending on the specific assay used, would suggest a bacterial infection, while a low procalcitonin level would favor a diagnosis of TB. The use of procalcitonin to guide antibiotic therapy has been shown to reduce antibiotic consumption and improve patient outcomes. In several studies, patients with respiratory infections who were treated with antibiotics based on their procalcitonin levels had shorter hospital stays, lower mortality rates, and lower rates of antibiotic-related adverse events compared to patients who were treated with antibiotics based on clinical judgment alone. Procalcitonin-guided antibiotic therapy can be particularly beneficial in patients with suspected bacterial pneumonia. In these patients, a high procalcitonin level would support the initiation of empiric antibiotic therapy, while a low procalcitonin level would suggest that antibiotics are not necessary. This approach can help to avoid the unnecessary use of antibiotics in patients with non-bacterial infections, such as TB. Antibiotic resistance is a growing global health threat. The overuse and misuse of antibiotics have led to the emergence of multidrug-resistant bacteria, which are difficult to treat and can cause serious infections. Procalcitonin can play an important role in antibiotic stewardship programs. By accurately identifying patients with bacterial infections, procalcitonin can help to ensure that antibiotics are used only when necessary. This can help to preserve the effectiveness of antibiotics for future generations. While procalcitonin is not typically elevated in patients with TB, there are some exceptions. In patients with severe TB or TB with

extrapulmonary involvement, procalcitonin levels may be elevated. Therefore, it is important to interpret procalcitonin levels in the context of the patient's clinical presentation and other diagnostic tests. In patients with suspected TB, a low procalcitonin level can help to rule out bacterial pneumonia. However, a high procalcitonin level does not necessarily rule out TB. In these cases, further investigations, such as sputum culture and molecular testing, are needed to confirm the diagnosis.[17,18]

The quest for accurate and rapid diagnostic tools for differentiating between pulmonary TB and bacterial pneumonia has led to the exploration of various biomarkers. Procalcitonin has emerged as a promising candidate in this pursuit, but it's crucial to understand its strengths and limitations in the context of other biomarkers and diagnostic tests currently used in clinical practice. Several biomarkers have been investigated for their potential to differentiate between TB and bacterial pneumonia, each with its own advantages and drawbacks. C-reactive protein (CRP) and interferon-gamma (IFN-γ) are two such biomarkers that have shown some promise in this regard. However, procalcitonin appears to possess several key advantages that position it as a potentially superior marker. CRP, an acute-phase protein produced by the liver in response to inflammation, is a widely used marker of infection and inflammation. While CRP levels are often elevated in bacterial pneumonia, they can also be elevated in TB and other non-infectious inflammatory conditions. This lack of specificity limits the utility of CRP in differentiating between TB and bacterial pneumonia. In contrast, procalcitonin demonstrates a more targeted response to bacterial infections, making it a more reliable indicator of bacterial etiology. IFN-γ, a cytokine produced by T lymphocytes, plays a crucial role in the immune response to Mycobacterium tuberculosis. IFN-γ release assays (IGRAs) measure the release of IFN-γ by T cells in response to specific M. tuberculosis antigens and are widely used for the diagnosis of latent TB infection. While IGRAs have high specificity for TB infection, they may not be as helpful in differentiating active TB from bacterial pneumonia. Furthermore, IFN-γ levels may not be elevated in all cases of active TB, particularly in patients with HIV co-infection or disseminated TB, which can limit its sensitivity. Procalcitonin, on the other hand, is less likely to be elevated in TB, making it a potentially more useful marker for differentiating between these two conditions. Procalcitonin's advantages extend beyond its superior specificity and sensitivity compared to CRP and IFN-γ. Its rapid kinetics, with levels rising within hours of the onset of bacterial infection, make it an ideal marker for acute settings. This rapid response allows for prompt diagnosis and timely initiation of appropriate therapy, which can be crucial in preventing complications and improving patient outcomes. Furthermore, procalcitonin levels correlate with the severity of bacterial infection, making it a useful prognostic marker. Higher procalcitonin levels have been associated with more severe disease and worse outcomes in various bacterial infections, including pneumonia. This information can help clinicians to identify patients at higher risk of complications and tailor their management accordingly. While procalcitonin holds significant promise as a diagnostic marker, it is essential to emphasize that it should not be used in isolation. The diagnosis of TB and bacterial pneumonia requires a comprehensive approach that integrates clinical findings, radiological imaging, and other laboratory tests. Chest radiography is a cornerstone in the evaluation of respiratory infections. It can provide valuable information about the location and extent of lung involvement, helping to differentiate between various pulmonary pathologies. However, chest radiographic findings in TB and bacterial pneumonia can often overlap, making it challenging to distinguish between these two conditions based on imaging alone. Sputum smear microscopy for acid-fast bacilli (AFB) remains a crucial test for the diagnosis of TB. While it has limitations in terms of sensitivity, particularly in patients with paucibacillary TB or HIV co-infection, it can provide a rapid and cost-effective way to identify patients with high bacterial loads.

Culture remains the gold standard for the diagnosis of TB and bacterial pneumonia. However, it can be time-consuming, taking several weeks to yield results. Molecular tests, such as PCR, offer a more rapid alternative and can provide valuable information about drug resistance. By integrating procalcitonin with these other diagnostic tests, clinicians can gain a more comprehensive understanding of the patient's condition and make more informed treatment decisions. For example, in a patient with respiratory symptoms and radiological findings suggestive of pneumonia, a high procalcitonin level would support the initiation of empiric antibiotic therapy. However, if sputum microscopy reveals AFB, the diagnosis of TB would be favored, and anti-TB treatment should be initiated promptly. The combination of procalcitonin with other biomarkers and diagnostic tests can further enhance the accuracy of diagnosis and improve patient management. For instance, in patients with suspected TB, a low procalcitonin level can help to rule out bacterial pneumonia, while a positive IGRA would further support the diagnosis of TB. In patients with suspected bacterial pneumonia, a high procalcitonin level, coupled with elevated CRP and a suggestive chest radiograph, would strengthen the diagnosis and guide antibiotic selection. This multifaceted approach, integrating clinical findings, radiological imaging, biomarkers, and microbiological tests, can lead to more accurate and timely diagnoses, facilitating prompt and targeted treatment.[19,20]

5. Conclusion

In conclusion, this research has underscored the potential of procalcitonin as a valuable biomarker for differentiating between pulmonary TB and bacterial pneumonia. The significantly elevated procalcitonin levels observed in patients with bacterial pneumonia compared to those with pulmonary TB highlight the potential of this biomarker to revolutionize the accurate and timely diagnosis of these two respiratory conditions. The ability to rapidly and accurately differentiate between TB and bacterial pneumonia holds paramount importance in clinical practice. Misdiagnosis can have dire consequences, leading to inappropriate treatment, delayed initiation of correct therapy, and potentially resulting in increased morbidity and mortality. Procalcitonin can effectively bridge this diagnostic gap and contribute to significantly improved patient outcomes. The stark contrast in procalcitonin levels observed between the two study groups highlights the distinct pathophysiological mechanisms underlying these infections. Procalcitonin possesses several advantages over other biomarkers and diagnostic tools currently used in the evaluation of respiratory infections. Procalcitonin demonstrates superior specificity compared to other inflammatory markers, such as C-reactive protein (CRP). Furthermore, procalcitonin's ability to differentiate between bacterial and non-bacterial infections can be particularly valuable in guiding antibiotic stewardship. The results of this study have profound implications for improving patient outcomes in the management of respiratory infections. By facilitating accurate and timely diagnosis, procalcitonin can help to avoid the pitfalls of misdiagnosis and inappropriate treatment. The potential benefits of procalcitonin are particularly significant in resource-limited settings, where access to advanced diagnostic tests may be limited.

6. References

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