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RESEARCH ARTICLE

Correlation of Procalcitonin with Acid Fast Bacilli and Gene Xpert MTB/RIF as a Marker of Treatment Progress in Pulmonary Tuberculosis patients

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ABSTRACT:
There are several limitations in using AFB and GeneXpert to evaluate the treatment of TB patients, one of which is influenced by sputum quality. Therefore, an alternative method is needed to help evaluate the treatment of TB patients. This study aimed to analyze the correlation of the Procalcitonin test with AFB and GeneXpert for evaluating the treatment of TB patients and the performance of Procalcitonin as a marker of TB patient treatment progress. A prospective cohort study was conducted from May to September 2022 at the West Nusa Tenggara General Hospital, Indonesia. Sputum and blood samples were collected from 36 patients who were confirmed positive for TB by GeneXpert MTB/RIF examination, then examined for procalcitonin and AFB before being given treatment and after the intensive phase of treatment. Procalcitonin tested with VIDAS Biomerieux and VIDAS BRAHMS PCT kit. Procalcitonin did not correlate with AFB (p=0.064, r= 0.327) and GeneXpert before treatment (p=0.169, r=0.245), but correlated with AFB (p=0.013, r=0.427) and GeneXpert MTB/RIF (p=0.020, r=0.405) after the intensive phase of treatment. Procalcitonin test with a cut-off value of 0.07 detected negative AFB cases after treatment with a sensitivity of 28.6 and a specificity of 96.2%. The procalcitonin cut-off value of 0.07 also detected negative Xpert MTB/RIF after treatment with a sensitivity of 16.7% and a specificity of 100%. The performance of Procalcitonin for detecting negative smear and negative Xpert MTB/RIF after the intensive phase of treatment is classified as having high specificity, but its sensitivity is still low. Future studies are needed to evaluate the performance of Procalcitonin compared to bacterial cultures.

KEYWORDS: Pulmonary tuberculosis; AFB; Xpert MTB/RIF test; Procalcitonin; Diagnostic Performance.

INTRODUCTION:

The number of new TB cases in Indonesia is still ranked third in the world and is one of the biggest challenges faced by Indonesia thus requires attention from all parties because it provides a high burden of morbidity and mortality. Early diagnosis and treatment are important for better prognoses[1-4]. TB treatment is one of the most efficient efforts to prevent the further spread of the bacteria that cause TB[5-8].

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Treatment was considered successful if evidenced by microscopic smear conversion at the end of the intensive phase (2 months)[9]. AFB conversion is a strong predictor for assessing treatment progress in pulmonary TB patients[10]. In most Low Middle-Income Countries, smear microscopy (AFB) is still the first line of diagnosis[11]. The purpose of smear microscopy is to detect acid-fast bacilli (AFB) in stained specimens. Smear microscopy has several limitations, such as: It has a sensitivity lower than molecular tests[12-14], and culture in expectorant sputum and induced sputum (29% compared to culture)[15], and low sensitivity in patients with low bacillary load in sputum[16]. This method cannot differentiate between *Mycobacterium tuberculosis* and non-tuberculous mycobacteria (NTM), and it is not

determined if bacilli are viable (alive) or non-viable (dead)[5]. In addition, smear microscopy cannot determine susceptibility of the bacilli to TB drugs.

World Health Organization (WHO) recommends GeneXpert MTB/RIF examination in new TB drug resistance suspected patients whose AFB results are still positive after the intensive phase of treatment. The Xpert MTB/RIF assay is a cartridge-based automated DNA test that accurately detects TB and mutation of rpoB gene associated with rifampicin resistance (RR) in less than 2 hours[17]. This assay can detect rifampicin resistance by detecting mutations in the rpoB gene using five different probes (A, B, C, D, and E)[18]. This method has a higher sensitivity when compared to the AFB smear and culture in respiratory specimens (sputum-smear positive: 99%, sputum smear negative: 68%)[15]. However, AFB and GeneXpert methods have several limitations, one of which is that the results of the examination can be influenced by the poor quality of the specimen (sputum)[11,19,20]. Accurate examination results depend on sample collection, handling, and storage[16,21]. Because Xpert MTB/RIF is not recommended for use in monitoring treatment[15], thus, simple and rapid marker for monitoring treatment response of pulmonary tuberculosis is needed if sputum samples are inadequate.

Several studies have shown that Procalcitonin can help predict treatment response and TB diagnosis[22,23]. PCT is a protein consisting of 116 amino acids with a molecular weight of 14.5 kDa encoded by the CALC-1 gene on chromosome 11[24,25]. Procalcitonin is a protein that is known to increase in response to sepsis due to bacterial infection and to a lesser extent due to mycobacterial infection. Bacterial infection is a strong stimulus for procalcitonin production, whereas if systemic inflammation is caused by a viral infection, procalcitonin induction will be low[26-28]. In pulmonary TB patients, pro-inflammatory cytokines are produced from T cells due to stimulation of *Mycobacterium tuberculosis* bacterial antigens such as interleukin-1 (IL-1), TNF-α, and other inflammatory cytokines are elevated[29,30]. The increase in these cytokines induces an increase in the expression of the CALC-1 gene in parenchyma cells resulting in the hypersecretion of procalcitonin[31,32]. The rapid procalcitonin test can help clinicians in early diagnosis of pulmonary tuberculosis in an effort to eradicate the disease[33].

Procalcitonin has been explored as a biomarker for diagnosing tuberculosis, and Procalcitonin levels also clearly associated with the risk of death in patients with tuberculosis[34,35]. Serum procalcitonin shows diagnostic and prognostic utility at the end of treatment of pulmonary TB patients[23]. In a low-burden TB setting, PCT may be of some value in distinguishing pulmonary TB from pneumococcal pneumonia[36]. Another study showed that procalcitonin levels decreased in pulmonary TB patients after undergoing treatment. However, no studies have investigated whether procalcitonin is a useful marker for monitoring the response to pulmonary TB treatment. In addition, there are no published studies addressing the sensitivity and specificity values of procalcitonin compared to AFB and GeneXpert as a predictive factor for pulmonary tuberculosis treatment progress. Therefore, this study aims to determine the relationship between Procalcitonin with AFB and GeneXpert before and after patients receive the intensive phase of treatment. It is also intended to determine the performance of the procalcitonin test in monitoring the progress of treatment in pulmonary TB patients.

MATERIALS AND METHODS:

Materials:

Xpert MTB/RIF cartridge purchased from PT. Medquest Jaya Global, Jakarta, Indonesia. The Mini Vidas tool for procalcitonin examination is available at the West Nusa Tenggara Provincial Hospital. Sputum and blood of TB patients were received as samples from hospitals and several health centers. All other materials have analytical levels that are already available at the West Nusa Tenggara Provincial Hospital.

Research Methods:

This cohort prospective study was conducted from May to September 2022 in West Nusa Tenggara, Indonesia. West Nusa Tenggara is one of the provinces in Indonesia which has a population of more than five million[37]. The study was conducted at 6 government short-term tuberculosis treatment sites that were systematically selected and directly observed. These sites mostly participate in TB screening, diagnosis, treatment monitoring programs, and laboratory services.

Data collection:

Characteristics of participants, comorbidities, and other factors were collected using patient medical record data and case report forms (CRF) by trained personnel through interviews.

Patient enrollment:

A total of 36 patients who were confirmed positive for TB by GeneXpert MTB/RIF who met the inclusion criteria were enrolled in this study as research subjects. However, those who were confirmed positive for drug-resistant TB, had comorbid diseases, and confirmed TB with positive X-rays were excluded. TB DOTS officers and TB Programmers provide patients with an explanation of the sample collection to be carried out. From each TB patient, two samples will be collected, that is blood and sputum samples before the patients were given anti-tuberculosis drugs. Blood and sputum samples were transported in a cool box to the clinical

pathology laboratory at West Nusa Tenggara General Hospital for laboratory examination. Sputum samples were stored at 2°C – 8°C until transported to the examination site. Samples were submitted to the clinical pathology laboratory to be examined for Procalcitonin and AFB smear microscopy.

After sample collection, each TB patient received intensive phase treatment (2 months). After that, the sample collection process was carried out again with the same steps as before. Blood samples that have been collected will be examined for procalcitonin levels, while sputum samples will be examined for AFB smear microscopy and GeneXpert MTB/RIF.

Quality assurance and quality control:
Strengthening the quality of the Procalcitonin *test* by using two controls contained in each Vidas Biomerieux PCT kit. Controls should be implemented immediately after a new kit is opened to ensure that the quality of the reagents is not compromised. If the control results are still within the specified value limits, then the examination results are said to be valid. Calibration can also be checked using this control. The tool will detect these controls as C1 and C2. Calibration is carried out using two calibrators, namely S1 and S2 which have been provided in the kit. Calibration must be carried out every time a new reagent is opened, every time master lot data is entered, or every 28 days. A proficiency testing schemes continuously monitored all study testing methods. Also, the West Nusa Tenggara General Hospital is a hospital that has been accredited by a Quality Accreditation Agency.

Laboratory investigation:
Sputum samples collected from each patient were divided into two; one for microscopic smear (AFB) testing using the Ziehl Neelsen method and one for the Xpert MTB/RIF test (Cepheid, Sunnyvale, California, United States). Measurement of Procalcitonin levels was performed using MINI VIDAS (Biomerieux, USA) and VIDAS PCT kit reagents.

Data entry and analysis:
Data entry was performed on Microsoft Excel 2010 software. Clean data was transferred to and analyzed using Jamovi software version 2.3.21. The characteristics of the study participants were analyzed using descriptive statistics. The differences of Procalcitonin levels in positive and negative smears, as well as differences in procalcitonin levels in positive and negative GeneXpert MTB/RIF were analyzed using the Independent Sample t-test if the data was normally distributed and using Mann-Whitney if the data was not normally distributed. The correlation of Procalcitonin with AFB and GeneXpert before and after treatment was analyzed by Rank Spearman test, $p < 0.05$ was considered statistically significant. Receiver Operating Characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of the Procalcitonin test against AFB and GeneXpert MTB/RIF.

RESULT:

Characteristics of study participants:
Most of the participants (20; 60.6%) were men (Figure 1A). The mean participant age was 45 years (Figure 1B). A total of 16 participants (48.5%) had a history of smoking (Figure 1C). Rifampicin drug resistance was not found in all participants. There were 3 participants who dropped out of the study due to several reasons, namely death and loss to follow up so that the number of subjects who took part in the study to completion was 33 subjects.

Figure 1A.

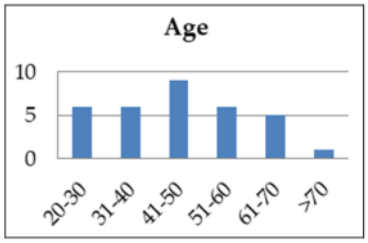

Figure 1B.

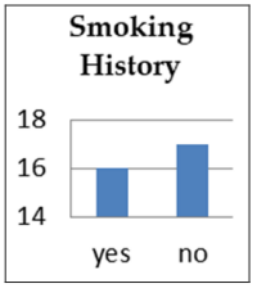

Figure 1C.

Description:
1A: Characteristics of TB cases by participant's gender
1B: Characteristics of TB cases by participant's age
1C: Characteristics of TB cases by participant's smoking history.

Table 1: Laboratory test results before and after the intensive phase of treatment

Variables	Before Treatment		After Intensive Phase of Treatment		*Wilcoxon Sign Rank test p-value*
	Frequency	%	Frequency	%	
Bacilli DNA quantification by Xpert MTB/RIF test :					*<0.001**
Negative	0	-	15	45.5%	
Very Low	7	21.2%	5	18.2%	
Low	8	24.2%	6	18.2%	
Medium	8	24.2%	6	18.2%	
High	10	30.3%	0---	-	
Acid Fast Bacilli (AFB) microscopy					*0.001**
Negative	17	51.5%	26	78.8%	
Scanty	1	3.0%	0	-	
+1	6	18.2%	5	15.2%	
+2	6	18.2%	2	6.1%	
+3	3	9.1%	0	-	
Procalcitonin (ng/mL)					*0.013**
≤ 0.05	22	66.7%	30	90.9%	
> 0.05	11	33.3%	3	9.1%	

*Wilcoxon Sign Rank test, $p < 0.05$ (Significant)

Table 2: Differences in Procalcitonin levels of positive and negative AFB and GeneXpert before and after treatment

Variable	Before treatment (p-value)		After intensive phase of treatment (p-value)	
	Acid Fast Bacilli (AFB)	GeneXpert MTB/RIF	Acid Fast Bacilli (AFB)	GeneXpert MTB/RIF
Procalcitonin (ng/mL) †	0.205	NA	0.052	0.111

†Wilcoxon Sign rank test (Jamovi 2.3.21)
NA: Not applicable

Laboratory Examination:

All participants had positive Xpert MTB/RIF test results at diagnosis (before treatment) with the highest percentage being 10 (30.3%), having a high bacillary load. There were 15 (45.5%) negative Xpert MTB/RIF results after the intensive phase of treatment and the rest were still positive (55.5%). The analytical test showed that there was a significant difference between the results of Xpert MTB/RIF before and after the intensive phase of treatment (Table 1).

A total of 16 (48.5%) participants had positive smear results at diagnosis and there was a decrease in the percentage to 21.3% after treatment was given. AFB conversion from positive to negative occurred in 9 participants, while AFB conversion remained positive in 7 study participants. Participants with smear positive results after the intensive phase of treatment did the continuation phase of treatment. Statistical analysis also showed significant differences in AFB before and after the intensive phase of treatment ($p = 0.001$).

Procalcitonin levels of Positive and Negative AFB and GeneXpert MTB/RIF:

There was no difference in procalcitonin levels in participants with positive and negative smears before ($p = 0.205$) and after the intensive phase of treatment ($p = 0.052$), and Procalcitonin levels in the positive and negative GeneXpert MTB/RIF test results showed no difference before and after the intensive phase of treatment ($p > 0.05$) (Table 2).

Correlation of Procalcitonin with AFB and GeneXpert MTB/RIF:

Of the 36 PTB patients enrolled in this study, 3 patients were excluded because they could not participate in the study until the end. Out of a total of 33 TB patients, 16 patients were positive for *Mycobacterium tuberculosis* with AFB smears, the rest were smear negative. Of the total 33 patients enrolled in this study, 11 patients (33.3%) had procalcitonin levels > 0.05 ng/mL before treament and and decreased to 9.1% after the intensive phase of treatment was given (Table 1).

Based on the results of statistical analysis of the correlation of each variable, it showed that Procalcitonin correlated with AFB ($p = 0.013$, $r = 0.427$), and GeneXpert MTB/RIF ($p = 0.020$, $r = 0.405$) after intensive phase treatment but had no correlation with AFB and GeneXpert before treatment ($p > 0.05$) (Table 3 and 4).

Table 3: Correlation between Procalcitonin with AFB and GeneXpert MTB/RIF before treatment

Variables	PCT-pre	
AFB pre	Spearman's rho	0.327
	p-value	0.064
GeneXpert MTB/RIF pre	Spearman's rho	0.245
	p-value	0.169

Abbreviations: PCT, Procalcitonin; AFB, Acid Fast Bacilli

Description:

2A: Plot correlation of Procalcitonin (pre) with GeneXpert MTB/RIF (pre)

2B: Plot correlation of Procalcitonin (pre) with AFB (pre)

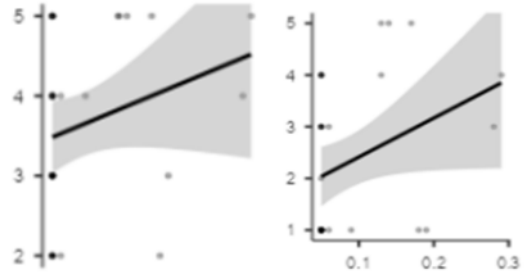

Figure 2A. **Figure 2B**

Table 4: Correlation between Procalcitonin with AFB and GeneXpert MTB/RIF after intensive phase of treatment

Variables	PCT-post	
AFB post	Spearman's rho p-value	0.427 0.013†
GeneXpert MTB/RIF post	Spearman's rho p-value	0.405 0.020†

† Significant, $p < 0.05$

Abbreviations: PCT, Procalcitonin; AFB, Acid Fast Bacilli

Description:

3A: Plot correlation of Procalcitonin (post) with GeneXpert MTB/RIF (post)

3B: Plot correlation of Procalcitonin (post) with AFB (post)

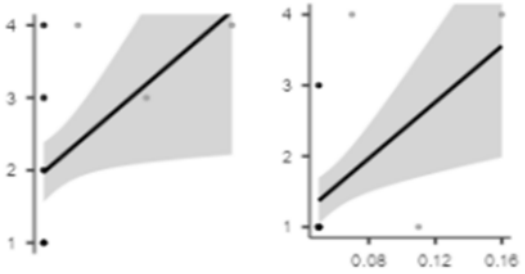

Figure 3 A. **Figure 3B.**

Description:

4A: Plot correlation of AFB and GeneXpert MTB/RIF before treatment

4B: Plot correlation of AFB and GeneXpert MTB/RIF after treatment

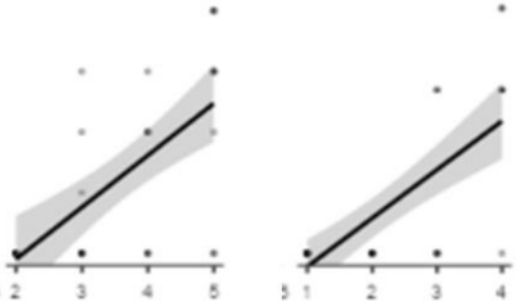

Figure 4A. **Figure 4B.**

Table 5: Correlation between AFB and GeneXpert MTB/RIF

Variables		GeneXpert MTB/RIF			
		Pre		Post	
		p-value	Spearman's rho	p-value	Spearman's rho
AFB	Pre	<0.001	0.652***		
	Post			<0.001	0.683***

Note: * p < .05, ** p < .01, *** p < .001

Table 5 above shows that AFB and GeneXpert have a moderate correlation both before (r = 0.652, p<0.001) and after the intensive phase of treatment (r = 0.683, p<0.001).

Cut-off value, sensitivity, and specificity of Procalcitonin levels:

Determining the cut-off value, sensitivity, and specificity of Procalcitonin for each variable was carried out using *Receiver Operating Characteristic* (ROC) curve analysis. ROC curve analysis was performed on the Procalcitonin variable against the AFB and GeneXpert MTB/RIF variable before and after the intensive phase of treatment. The results of the analysis showed various *Area Under Curve* (AUC) values with a p-value > 0.05, which means that these results did not describe the ability of serum Procalcitonin to AFB and GeneXpert MTB/RIF to be used as diagnostic markers and markers of treatment progress in Pulmonary TB patients (Table 6).

Table 6: Performance of Procalcitonin for AFB (positive and negative) and GeneXpert MTB/RIF (positive and negative) before and after treatment

Variables	Procalcitonin							
		AUC	p-value	Cut-off	Sensitivitas (%)	Spesifisitas (%)	PPV (%)	NPV (%)
AFB-pre[a]	Positive	0.610	0.280	0.06	43.75	76.47	63.64	59.09
AFB-post[b]	Negative	0.624	0.322	0.07	28.57	96.15	66.67	88.33
GeneXpert MTB/RIF-post[c]	Negative	0.583	0.416	0.07	16.67	100	100	50

Note: p-value < 0.05 = Significant

[a]Procalcitonin performance against smear positive for TB diagnosis before being given treatment

[b]The performance of procalcitonin against smear negative to predict the progress of intensive phase treatment

[c]The performance of procalcitonin against GeneXpert MTB/RIF was negative for predicting intensive phase treatment progress

DISCUSSION:

Sputum quality affects the detection of bacillary tuberculosis that causes pulmonary TB using either the AFB or Xpert MTB/RIF methods[19,38,39]. Many studies have considered the role of Procalcitonin in differentiating TB infection from other bacterial infections, besides that other studies have also shown the role of serum procalcitonin as a predictor of treatment response in pulmonary TB patients[22,23,31]. Intracellular microbial infections such as MTB tend to induce a Th1-type response to secrete IFN-γ which in turn activates macrophages. These active macrophages will release pro-inflammatory mediators (TNF-α, IL-1β, IL-6, IFN-γ, IL-2, IL-8) and anti-inflammatory (IL-10, IL-4, IL-13) simultaneously[40]. An increase in pro-inflammatory mediators induces an increase in CALC-1 gene expression in parenchymal cells resulting in Procalcitonin hypersecretion[31].

In the present study, Xpert MTB/RIF and AFB were significantly correlated with Procalcitonin after treatment ($p < 0.05$) and Procalcitonin levels also showed a decrease after the intensive phase of treatment was given. This suggests that procalcitonin can be used as a predictor of treatment response in pulmonary TB patients. This is also supported by the specificity value of Procalcitonin which is relatively high (96.2%) for smear-negative and 100% for GeneXpert MTB/RIF-negative after treatment was given. The decrease in procalcitonin levels after intensive phase treatment could be due to the inhibitory effect of anti-tuberculosis drugs. The four anti-tuberculosis drug regimens have different mechanisms of action. Rifampicin (RIF) acts by inhibiting bacterial RNA polymerase activity in susceptible organisms without affecting human cell RNA polymerase[41-43]. Isoniazid (INH) inhibits a reductase required for the synthesis of a long-chain fatty acid called mycolic acid which is an important constituent of the mycobacterial cell wall[42,44]. Ethambutol acts by inhibiting the synthesis of arabinogalactan, which serves as a link between mycolic acid and peptidoglycan in organisms and diffuses into the cells of tubercle bacilli and inhibits metabolism[41,42,45]. Pyrazinamide (PZA) is a bactericidal drug that acts by inhibiting fatty acid synthesis and preventing mycolic acid synthesis. It is converted to the active intermediate, pyrazinoic acid, by amidase in mycobacteria[42,46,47].

Due to the administration of these 4 drug regimens, the pro-inflammatory mediators released due to the induced MTB bacteria will decrease which will affect the levels of procalcitonin secreted. On the other hand, this study showed that Xpert MTB/RIF and AFB did not correlate with Procalcitonin. This shows that procalcitonin cannot be used as a diagnostic marker for TB. This is also supported by the performance of Procalcitonin in this finding which states that procalcitonin sensitivity is low (43.75%) in diagnosing TB. This may be due to the pattern of cytokines secreted within the TB infection itself, in which high amounts of IFN-γ are found in newly infected pulmonary TB patients[48]. Based on in vitro observations, IFN-γ inhibits the secretion of Procalcitonin from adipose tissue[49]. Anti-inflammatory mediators such as IL-10 were also found to be higher in pulmonary TB patients[50]. IL-10 strongly inhibit the production of proinflammatory cytokines such as IL-1, IL-6, and TNF by monocytes or macrophages[51]. By inhibiting pro-inflammatory cytokines, the stimulus for procalcitonin synthesis is also inhibited, which affects the levels of procalcitonin secreted. In other words, the release of IL-10 during TB infection suppresses the synthesis and secretion of procalcitonin. Although the AFB and GeneXpert MTB/RIF tests were positive, they had no effect on the resulting Procalcitonin levels. This shows that procalcitonin levels do not depend on the number of MTB bacteria but are determined by the cascade of inflammatory cytokines released during infection[52].

Another finding in this study was that there was a correlation between AFB and GeneXpert MTB/RIF both before and after the intensive phase of treatment. Several publications have reported the correlation between semi-quantitative results from GeneXpert MTB/RIF and AFB[53]. This positive correlation makes GeneXpert's semi-quantitative results useful for estimating a patient's infectious potential and for guiding airborne isolation strategies when integrated with other clinical features in a smear independent algorithm[54–56]. These findings indicate that GeneXpert can be used as a test for monitoring the treatment outcomes of pulmonary TB patients. However, PCR-based tests cannot differentiate between dead and live bacilli because PCR can detect DNA from bacilli that are not viable after administration of anti-tuberculosis drugs or from a history of previous TB, which can affect the specificity of the test[57–59].

The performance of procalcitonin against smear and GeneXpert MTB/RIF for diagnosing and monitoring the progress of treatment of TB patients did not show significant results ($p > 0.05$) with various sensitivity and specificity values. However, these findings indicate a tendency to decrease Procalcitonin levels followed by a decrease in AFB and GeneXpert MTB/RIF positivity. The ability of any diagnostic test using sputum specimens to detect TB depends on the quality of the specimen collected.

CONCLUSION:

Procalcitonin can be considered as a biomarker to monitor the response of treatment of TB patients, but the performance of the procalcitonin test for detecting TB at the end of the intensive phase of treatment is low. Future

studies may be conducted to see the performance of procalcitonin when compared with more sensitive assays. Using a more sensitive and specific test for comparison may also result in better performance on the procalcitonin test. We recommend serum procalcitonin test as a predictor of treatment response in pulmonary TB patients regardless of the performance of the procalcitonin test.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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