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ORIGINAL ARTICLE

Performance of clinical scoring and microscopic combinations for diagnosing pulmonary tuberculosis with the GenXpert criteria

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ABSTRACT

Pulmonary tuberculosis is a prominent health issue in Indonesia, which ranks second in the world regarding the number of patients. Rapid tuberculosis detection is crucial for early treatment, a better prognosis, and a reduction in disease transmission; however, the availability of molecular rapid tests is limited. Cross-sectional design and retrospective analyses of pre-pandemic data from 723 patients with suspected pulmonary tuberculosis from 2017 to 2019 were conducted in this study. The study aimed to assess the performance of clinical scoring and microscopic examination in tuberculosis diagnosis at RSUD Sayang Cianjur. The effectiveness of sequential (two-stage) and simultaneous combinations of clinical scoring and sputum smear microscopic were investigated. Performance assessments consisted of 2x2 tables, calculation according to Gordis, and Receiver Operator Characteristic (ROC) analysis, with GenXpert results as the gold standard. The results showed lower performance of the individually performed scoring system, with clinical scoring having a sensitivity of 34.44% and a specificity of 97.15%. Microscopic Acid Fast Bacteria (AFB) had a sensitivity of 70.20% and a specificity of 98.57%. The net sensitivity of the sequential combination was 28.48%, and the specificity was 99.05%. The net sensitivity of the simultaneous combination was 77.15%, and the specificity was 95.72%. The area under the curve from the sequential diagnostic method was 0.728, and the area under the curve of the simultaneous diagnostic was 0.884. The sequential and simultaneous combinations of clinical scoring and the AFB microscopy improved the test performance. The simultaneous combination performed slightly better than the sequential combination.

Keyword: Acid Fast Bacteria, Clinical scoring, Molecular Tuberculosis Test, Sequential Combination, Simultaneous combination

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INTRODUCTION

Pulmonary tuberculosis (TB) is one of the significant health problems in Indonesia. Globally, Indonesia ranks number two as the country with the highest number of tuberculosis patients. [(1)] This shows the need to improve many aspects of health services in Indonesia. The large number of pulmonary tuberculosis cases implies morbidity, mortality, and a subsequent increase in disease transmission. Pulmonary tuberculosis findings require reliable diagnostic tools. The molecular rapid test is available in many laboratories in Indonesia since the Indonesian Ministry of Health provides the test in numerous districts. The test is fast reliable, and reduces the human factor errors that emerge in earlier diagnostic methods.[(2,3)] The molecular rapid test for tuberculosis also provides information regarding the sensitivity of the microorganism to drugs used in tuberculosis treatment,[(4)] and it has valuable advantage for extrapulmonary tuberculosis.[(5)] Despite the methodology advantages of the rapid molecular test, the test requires expensive pre-installment investment before the implementation of the test in the laboratory. [(6,7)] The investment consists of human resources training and the provision of machines and reagents. [(8,9)] Although molecular testing for TB has improved diagnosis, it is still not widely available in many of our healthcare facilities. Even when they are accessible, molecular test utilization for tuberculosis diagnosis is still low. [(10)] The significant investment was not attainable for some districts, so there were districts without tuberculosis rapid molecular testing, and they relied on clinical and microscopic examination to diagnose pulmonary tuberculosis.[(11-13)] In environments with limited access to on-site diagnostic tests, radiography, and specialist staff, rapid treatment of TB is challenging.[(13)]

In circumstances with a significant probability of loss to follow-up, the discovery of a rapid method to detect tuberculosis is a crucial factor. Patients with pulmonary tuberculosis would benefit significantly from immediate treatment. They will have a better prognosis and the transmission rate of the disease will decline considerably in the community.[(1,14)] Clinical data largely determined pulmonary tuberculosis diagnosis. The majority of the additional tests required clinical judgment. A scoring system to diagnose tuberculosis in pediatric patients is widely used [(15)], whereas clinical scoring in adult patients is still being developed and studied.[(16-18)] One of the clinical scoring systems to diagnose TB among adult patients was developed by a research team from Johns Hopkins University and Uganda.[(16)] The scoring system aimed to predict the active state of tuberculosis among suspected patients. It was developed from clinical data, and the validation was made available by comparing the score with the rapid molecular test as the gold standard. A score 5 in the scoring system could predict 9-25% of the active TB patients, depending on the pretest probability of the institution where the test was performed. The scoring system could help predict whether the tuberculosis therapy is better to be performed or whether it is needed to delay the therapy until further diagnostic measures prove the need to initiate the it.[(16)] Microscopic examination is a diagnostic test that requires less financial investment than a rapid molecular test. The Ziehl Nielsen stain and trained human resources are readily available in the Community Health Center, or Puskesmas, in Indonesia.[(10)] The test was the primary diagnostic tool to diagnose tuberculosis before a rapid molecular test for tuberculosis was discovered. Microscopic test has its limitation, such as the low sensitivity[(19)], despite the ease of use and affordability. This study aims to investigate the performance of clinical scoring and microscopic examination. A combination of sequentially or simultaneously combined tests is proposed to improve

the performance of the test and hopefully could resolve the problem of tuberculosis diagnosis when the rapid molecular test is unavailable.

METHODS AND SUBJECTS

The study was utilizing a cross-sectional design to investigate the performance of clinical scoring and AFB microscopic in tuberculosis diagnosis. The research was done in RSUD Sayang Cianjur, which is the city's secondary hospital. We studied laboratory data and medical record data of the adult patients suspected of having pulmonary tuberculosis who were referred to the hospital by a primary health care provider, such as Puskesmas or a health clinic in Cianjur. We used pre-pandemic data, from 2017 to 2019 to obtain a more precise investigation. During the outbreak of SARS-COV-2 pandemic, the tuberculosis examination significantly decreased in number, especially the microscopic data. Patients who were included in the study were those who had undergone the clinical examinations, such as sputum microscopic AFB examination and rapid molecular testing. Clinical data consist of the patients' demographic data, the history of the disease progression, and the signs of the disease which can be captured during the physical examination. The clinical data, including age, gender, comorbidity, such as HIV infection status and diabetes, existed symptoms (cough, breathlessness, fever, weight loss, night sweat) and duration of symptoms, were obtained from the medical record of the patients. This study utilized clinical scoring proposed by Baik et al. (2020)[16], which has been validated in a large population multicentric study in Uganda. Microscopic data were extracted from laboratory records. The microscopic examinations were performed on slides of sputum smears that had been stained according to the Ziehl Nielsen method. Data from rapid molecular test examinations were extracted from laboratory data. The molecular rapid test available in the hospital was GeneExpert™. The performance of the diagnostic tests combination was assessed by the methods described by Gordis et al. (2014), [20] by 2x2 tables, and by ROC analysis.

A combination of the tests, either sequentially or simultaneously, was expected to elevate the diagnostic performance needed to diagnose active pulmonary tuberculosis among suspected patients. . Sequential combinations utilize the scoring system as the first-line test. When the first-line test reveals a positive result, the secondary test, the AFB microscopic examination, is performed. The diagnostic decision will then be determined by the AFB microscopic reading. The simultaneous combination performs the clinical scoring system and AFB microscopic reading at the same time. The decision will be based on any test revealing a positive result, including clinical scoring or AFB microscopic examination. We used two analysis methods to investigate the performance of the test combinations. The first method was the calculation of the simultaneous and sequential combination test performances. The calculation was performed based on the method described by Gordis et al., as shown in Figure 1. The second method was the Receiver Operator Characteristic (ROC) method to investigate the area under the curve of the combination. For the calculation and ROC method, we employed cutoff 4 from the scoring system based on the distinction of the tuberculosis positive probability in RSUD Sayang.

Sequential screening test
Net Sensitivity = (Sensitivity of clinical scoring) x (Sensitivity of AFB)
Net Specificity = (Specificity of clinical scoring + Specificity of AFB) - (Specificity of clinical scoring x Specificity of AFB)

Simultaneous screening test
Net Sensitivity = (Sensitivity of clinical scoring + Sensitivity of AFB) - (Sensitivity of clinical scoring x Sensitivity of AFB)
Net Specificity = (Specificity of clinical scoring) x (Specificity of AFB)

Figure 1. Calculation of Net Sensitivity and Net Specificity According to Gordis et al[20]

The study has been approved by the Ethical Committee of UNJANI Medical Faculty, and the letter of approval had been released. The release number of ethical approval letter was 031/UM1.09/2020.

RESULTS AND DISCUSSION

During 2017-2019, there were 723 complete cases of suspected pulmonary tuberculosis in RSUD Sayang Cianjur. The patients were examined clinically (history taking and physical examinations), the sputum was examined microscopically to investigate the presence of AFB, and a biomolecular examination was performed with rapid molecular test. The group consisted of 442 males and 281 females. 18 individuals (2.4%) with tuberculosis patients were also diagnosed with HIV. In addition, 16 people (2.2%) of the suspected tuberculosis patients had diabetes mellitus as a comorbid.

We investigated the performance of the individual tests, with the rapid molecular test as the gold standard. The clinical scoring employed the history-taking and physical examination data of suspected pulmonary tuberculosis patients. Judgement of positivity was based on whether the total score exceeded the cut-off or not. Baik et al. differentiated the cut-off usage based on positive probability in the study area.[16] We used a cut-off score of 4 to determine positivity (whether the patient is positively or negatively categorized as having active pulmonary tuberculosis). The cut-off was chosen because, based on the positivity data, it was estimated that the positive probability test was 15% in RSUD Sayang Cianjur. Our study showed that the scoring system had a lower performance when applied to our study population. The sensitivity of the clinical scoring was 34,44%, and the specificity was 97,15%. The performance of AFB alone to determine the positivity of active pulmonary tuberculosis was also determined with the rapid molecular test as the gold standard. Our study found that the microscopic AFB sensitivity was 70.20% and the specificity was 98.57%. Figure 2 shows the 2x2 tables of the clinical scoring system and the AFB microscopic. The individual test performance showed that both tests (Clinical scoring and microscopic AFB) had good specificity but lack sensitivity, especially the clinical scoring one.

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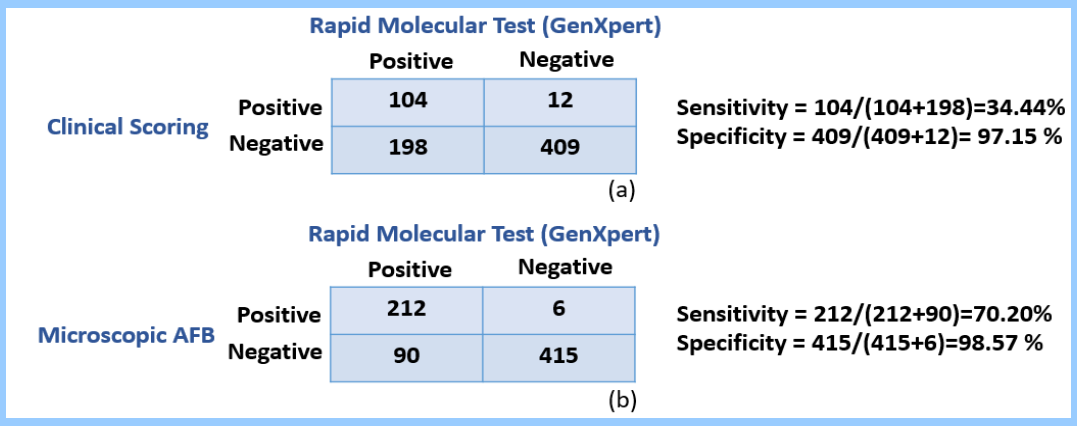


Figure 2. The 2x2 tables of the clinical scoring system (a) and the AFB microscopy (b) the rapid molecular test, the GenXpert, as the gold standard.

Diagnostic decision using the sequential combination method utilized the two-step decision making. In the sequential combinations, the scoring system was the first-line test and the secondary test was the microscopic AFB. The diagnostic decision was determined by the AFB microscopic reading. The simultaneous combinations utilized the clinical scoring system and AFB microscopic reading at the same time. The decision was determined by any test revealing a positive result, either clinical scoring or AFB microscopy. From the individual tests sensitivity and specificity, we performed calculations to obtain the net sensitivity and net specificity of the sequential and simultaneous combinations according to the Gordis et al. formula.[20] The formula for the calculations can be seen in Figure 1. The calculation results for the sequential combination were net sensitivity of 24.17% and net specificity of 93.80%. Meanwhile, The calculation results for the simultaneous combinations [20] were the net sensitivity of 23.12% and the net specificity of 95.76%.

We investigated the performance combination of the test with the rapid molecular test as the gold standard. Using the sequential diagnostic decision method, we observed a decrease in the true positive results compared to the results from clinical scoring alone or AFB microscopic alone. In contrast with the sequential diagnostic decision method, we observed a higher number of true positive results in the simultaneous diagnostic decision method. The simultaneous diagnostic decision method yielded higher positive results than the clinical scoring alone or the microscopic AFB alone. The true negative results were higher in the sequential diagnostic decision method compared to those performed with the simultaneous method. The net sensitivity of the sequential diagnostic decision method was 28.48%, and the specificity was 99.05%. The net sensitivity of the simultaneous diagnostic decision method was 77.15%, and the specificity was 95.72%. Figure 3 shows the 2x2 of the sequential and the simultaneous combination diagnostic decision methods.

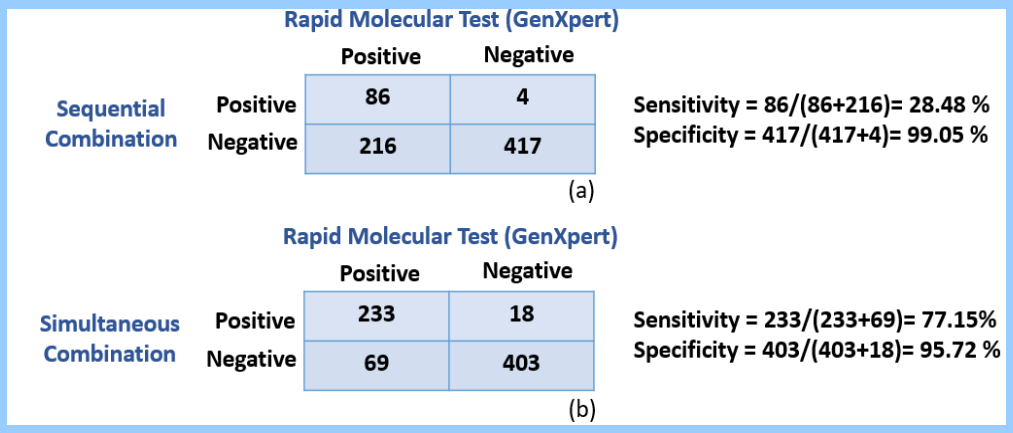


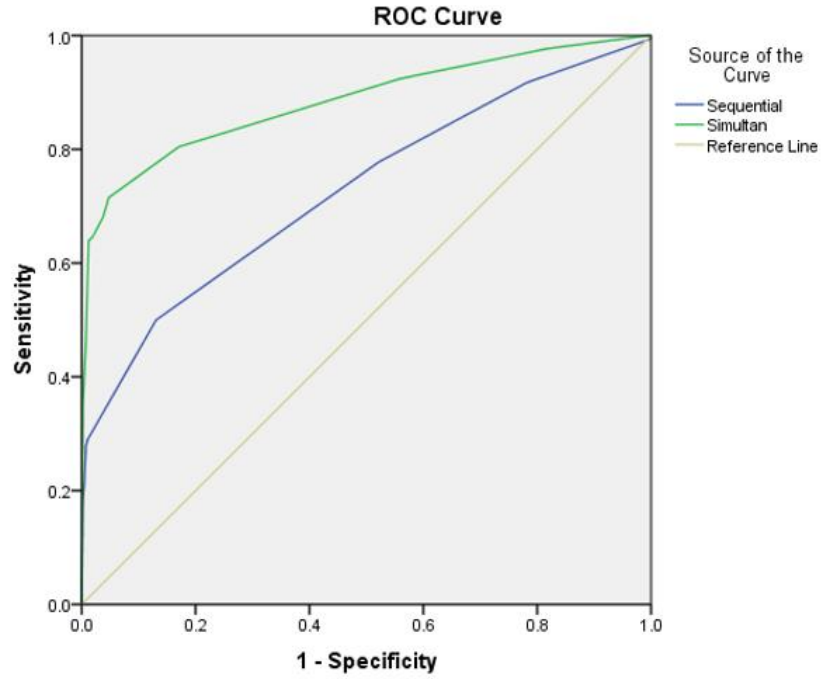
Figure 3. The 2x2 tables of the sequential combination diagnostic decision method (a) and the simultaneous combination diagnostic decision method (b)(rapid molecular test GenXpert as the gold standard)

We performed the ROC analysis to investigate the combination method that gives the largest area under the curve (AUC). The AUC is frequently used to assess the accuracy of diagnostic procedures. The test's increased as the ROC curve approached the upper left corner of the graph because the sensitivity rate was 1, and the false positive rate was 0, resulting in a specificity of 1). Thus , the AUC rate of 1.0 was the ideal ROC curve value. If graph is constructed on the 45° diagonal (y = x) of the ROC curve (AUC = 0.5) when the coordinates of the x-axis (1 - specificity) and the y-axis correspond to 1: 1 (i.e., true positive rate = false positive rate), this is equivalent to assessing the presence or absence of disease through an unintentional means, like a coin toss, which has no significance as a diagnostic tool. [21] Figure 4 explains how to interpret AUC.

Area under the curve (AUC)	Interpretation
0.9 ≤ AUC	Excellent
0.8 ≤ AUC < 0.9	Good
0.7 ≤ AUC < 0.8	Fair
0.6 ≤ AUC < 0.7	Poor
0.5 ≤ AUC < 0.6	Fail

Figure 4. Interpretation of Area Under The Curve [21]

The AUC needs to be higher than 0.5 for a diagnostic test to be considered useful. Figure 5 shows the curves that reveal the area under the curve of sequential and simultaneous methods. Both graphs were constructed above the diagonal 45° line. The graph position indicates that the AUC of sequential combination and simultaneous combination were higher than 0.5.



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Sequential	.728	.020	.000	.690	.767
Simultan	.884	.014	.000	.857	.911

Figure 5. The area under the curve of sequential and simultaneous methods

The AUC from the sequential diagnostic method was 0.728 (0.7 ≤ AUC≤ 0.8). The AUC of the sequential diagnostic method shows that the performance of the combination to diagnose pulmonary tuberculosis was fair. The AUC from the simultaneous diagnostic method was 0.884 (0.8 ≤ AUC≤ 0.9). The AUC of the simultaneous combination led us to the recognition that the simultaneous combination had good performance to diagnose pulmonary tuberculosis.

Rapid molecular test for tuberculosis detection has become the new standard for tuberculosis diagnosis. The test can be performed in a shorter time than the conventional method and detect amplified genetic material, this feature largely decreases the possibility of false positive results.[13] Despite the advantages of rapid molecular detection, the test also has some limitations. The cost of detection kits, the cost to implement the machine, and the waste management of used detection kits have become an obstacle to the use of rapid molecular technic in tuberculosis detection.[8] For the aforementioned reasons, clinical data and conventional laboratory tests still become the mainstay diagnostic method for tuberculosis.[15]

Clinical scoring has been widely used in tuberculosis diagnosis among the pediatric population. There were some studies aimed to investigate the use of clinical scoring in tuberculosis diagnosis among the adult population.[16-18] Baik et al. proposed a clinical scoring to diagnose

tuberculosis among the adult population. The scoring was validated in the western African population and it was said to have good performance. [16] The use of the scoring system among the non-African population hasn't been found so we assume that this study is the first to investigate the use of the Baik et al.'s scoring system among the non-African population. Conventional microscopic AFB test is still considered to be an important diagnostic test for tuberculosis diagnosis. Laboratory personnels in many primary health care in Indonesia have been extensively provided with training on microscopic examination to enable them to perform the examination. Most of the pulmonary tuberculosis cases in primary health care can be detected with AFB microscopic tests.[15] The cost needed to perform AFB microscopic tests is also lower than the cost of a tuberculosis rapid molecular test.[13] The advantage of using rapid molecular tests is the exceedingly higher sensitivity than the AFB microscopic test,[12] but the system faces a challenge in terms of pre-installation requirement, the scarcity of the machine, and the need for consumables, which make it difficult to provide the method in many primary health care facilities. Paucibacillary of the AFB is the most common problem encountered in microscopic and rapid molecular diagnostic method. [19]

It was shown from our study that AFB microscopic reached 98.57% of the specificity, while the specificity of clinical scoring was 97.15%. The net specificity of the simultaneous combination was 95.72%, and the net specificity of the sequential combination was 99,05%. Our study has shown that AFB microscopic reached 70.20% of sensitivity, while the sensitivity of clinical scoring was 34,44%. The net sensitivity of the simultaneous combination was 77.15% and the net sensitivity of the sequential combination was 28.48%. The area under the curve of clinical scoring and AFB microscopic in simultaneous combination was 0.884 as generated by ROC analysis. The same analysis aforementioned, generated area under the curve of 0.728 for clinical scoring and AFB microscopic in sequential combinations. Our study revealed that clinical scoring in the simultaneous combination with AFB microscopic seems to complement and enhance the performance of both tests. Thus, it can be said that the simultaneous combination method can be offered as diagnostic method in places where rapid molecular test is not readily available.

CONCLUSION

The combination of clinical scoring and AFB microscopic may enhance test performance, with the sequential combination enhancing specificity and the simultaneous combination theoretically enhancing sensitivity.[20] Our study supported the initial hypothesis, indicating that the combination of clinical scoring and AFB microscopic had a better test's performance compared to the individually performed tests. The manner of the combinations determined the aspect of performance to be enhanced. The sequential combination enhanced the specificity of the test, while the simultaneous combination enhanced the sensitivity of individual tests. The simultaneous combination performed better than sequential combination for pulmonary tuberculosis detection.

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DECLARATION OF INTEREST

Authors declares no conflicting interests.

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