Original Article

Diagnostic Accuracy and Clinical Utility of InaTB-Rif, Locally Developed Molecular Test for Tuberculosis, in Comparison with Xpert MTB/RIF in Indonesia

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Abstract

Background: Tuberculosis (TB) remains a significant public health issue in Indonesia. Early and accurate diagnosis and drug susceptibility testing are essential for TB management. This study compared the diagnostic accuracy of the locally developed InaTB-Rif molecular test and Xpert MTB/RIF, using Mycobacterium Growth Indicator Tube (MGIT) culture as the reference standard.

Methods: A cross-sectional study was conducted at Persahabatan Hospital, Jakarta, from February to August 2023. Presumptive pulmonary TB patients were recruited and tested using Xpert MTB/RIF, InaTB-Rif, and MGIT culture. The study assessed the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and agreement between InaTB-Rif and Xpert MTB/RIF for *Mycobacterium tuberculosis* (MTB) detection and rifampicin resistance. Diagnostic accuracy was compared using receiver operating characteristic (ROC) curves.

Results: MGIT culture identified 29 TB-positive and 26 TB-negative cases. InaTB-RIF showed a sensitivity of 93.1% (95% CI=0.77-0.99), specificity of 76.9% (95% CI=0.56-0.91), PPV of 81.8% (95% CI=0.64-0.93), and NPV of 90.9% (95% CI=0.70-0.98). Xpert MTB/RIF had a sensitivity of 89.7% (95% CI=0.726-0.978), specificity of 80.8% (95% CI=0.606-0.93), PPV of 83.9% (95% CI=0.66-0.94), and NPV of 87.5% (95% CI=0.67-0.97). The area under the curve (AUC) was 0.8501 for InaTB-RIF and 0.8521 for Xpert MTB/RIF, with no significant difference in accuracy (*P*=0.965). The kappa value for MTB detection was 0.776, indicating substantial agreement, while the kappa value for rifampicin resistance detection was 0.517, indicating moderate agreement.

Conclusions: InaTB-RIF demonstrates comparable diagnostic accuracy to Xpert MTB/RIF with good diagnostic performance and agreement for detecting MTB and moderate agreement for rifampicin resistance detection.

Keywords: InaTB-RIF, molecular diagnostic test, rifampicin resistance, tuberculosis diagnosis, Xpert MTB/RIF

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Submitted: January 9th, 2025
Accepted: April 22nd, 2025
Published: April 23rd, 2025

J Respirol Indones. 2025
Vol. 45 No. 2: 136-43
https://doi.org/10.36497/jri.v45i2.907

INTRODUCTION

Tuberculosis (TB) is an issue worldwide, especially in Indonesia, which ranks second among countries with the highest TB burden after India, with more than 1 million cases a year.[1] The End TB Strategy established milestones for substantially reducing TB mortality, incidence, and catastrophic costs by 2025. The initial step focuses on delivering integrated, patient-centered care and prevention, which includes early TB diagnosis and universal drug susceptibility testing (DST).[2]

Access to diagnostics has been recognized as a major problem, especially in many high-TB-burden countries. In 2023, it is revealed that only 62% of globally reported pulmonary TB cases were confirmed bacteriologically, and only 48% were tested with a World Health Organization (WHO)-recommended rapid diagnostics (WRD) as an initial test.[3]

The limited coverage of bacteriological confirmation for TB increases the risk of misdiagnosis, unnecessary treatments, and delays in accurate diagnosis, potentially resulting in higher morbidity and mortality. A significant outcome of the inadequate use of WHO-recommended rapid diagnostics (WRDs) is a substantial gap in detecting drug-resistant TB cases.[4]

Regarding this focus, WHO developed a standard for rapid detection modalities for diagnosing tuberculosis with high accuracy (an error rate less than 5%), reduced the time to treatment initiation (turn-around time (TAT) for receiving results of less than 48 hours for at least 80% of received samples), impactful towards patient-important outcomes, and cost-effective.

Currently, molecular-based tests such as Xpert play a crucial role in TB diagnosis and management. Several studies reported the beneficial impact of Xpert for TB diagnosis, especially in increasing the rate of bacterial confirmation, detection of drug resistance, and reducing time to detection,[5] and time to treatment initiation.[6] Its high accuracy, ability to detect rifampicin resistance, and practical advantages—including rapid processing and relatively good biological safety—establish Xpert as a primary diagnostic modality for TB.[7,8] However, expanding the availability of Xpert testing remains a challenge in many countries.

Cazabon et al reported that, as of 2016, the ratio of smear microscopy to Xpert services in 21 countries was approximately six to one.[9] At the national level, the study by Agredo and Osorio[10] found that in Colombia between 2013–2019, the coverage of Xpert only reached an average of 10.3%, with annual variation ranging from 0.2% to 23%.

Meanwhile, a study by Nalugwa et al in Uganda found that only 26% of suspected TB patients were referred for Xpert-based testing, with several factors contributing to the limited access to Xpert, such as lack of mobile connectivity, limited refrigeration, few centers with sputum transport modalities, and non-functionality of several machines.[11] Regarding these issues developing rapid molecular diagnosis tools locally will be useful in increasing diagnosing tools locally will be useful in increasing diagnosing capacities and expanding TB diagnosis centers.

In Indonesia itself, as of June 2024, data shows that 2,340 Xpert machines have been distributed across 2,110 healthcare facilities in Indonesia, with 1,288 of these machines located in primary healthcare facilities, covering 12.5% of all primary healthcare facilities in the country. Significant limitations in TB diagnostic access persist, particularly in remote regions, due to infrastructure gaps, limited diagnostic coverage, and insufficient laboratory capacity.[12]

Although WHO has recommended additional molecular platforms, such as Truenat, that developed in India, their field implementation remains limited, highlighting the ongoing gap between available technologies and real-world accessibility. Considering this, the development of alternative molecular diagnostic modalities is necessary, particularly those that can be developed domestically. This purpose is aligned with Indonesia's National Strategic Plan 2020-2024, which encourages all stakeholders, including industry, to develop a locally available rapid molecular machine for TB diagnosis.[12]

Regarding this issue, we evaluated the diagnosis accuracy of a rapid molecular machine using polymerase chain reaction (PCR) technique, named InaTB-Rif, compared to Xpert MTB/RIF, with Mycobacterium Growth Indicator Tube (MGIT) *Mycobacterium tuberculosis* (MTB) culture as gold standard. We also evaluated the agreement of rifampicin susceptibility of InaTB-Rif and Xpert MTB/RIF.

METHODS

This study was a cross-sectional study conducted at Persahabatan Hospital, Jakarta, Indonesia, from February to August 2023. Adult presumptive pulmonary TB patients at Persahabatan Hospital were assessed for recruitment. Patients who were unable to expectorate phlegm, on TB treatment for more than one month, or pregnant were all

excluded. We evaluated signs and symptoms of TB, history of TB treatment, and comorbidities, followed by a digital chest X-ray. All patients who provided a written consent form were tested for Xpert MTB/RIF assay, InaTB-Rif assay, Mycobacterium Growth Indicator Tube (MGIT) MTB culture, and drug susceptibility test (DST). Ethical approval was issued by the Ethics Committee for Health Research of Persahabatan Hospital (14/KEPK-RSUP/02/2023). We collected sputum in three tubes for Xpert MTB/RIF assay, InaTB-Rif assay, and MGIT culture in parallel.

The Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA) is a completely automated nucleic acid amplification test (by quick, real-time PCR). The rpoB gene's MTB-specific sequence served as the target and was marked with molecular beacons for changes in the area that determines rifampin resistance. The testing was done using the Xpert MTB/RIF assay test device platform according manufacturer's instructions, which completely integrates and automates sample preparation, amplification, and detection to make molecular testing simpler. Before a certain volume of the clinical samples was transferred to a cartridge containing all the reagents, a bacterial buffer was added to the samples. The Xpert MTB/RIF assay gadget was then equipped with the plastic cartridge, which delivered outcomes in under two hours.

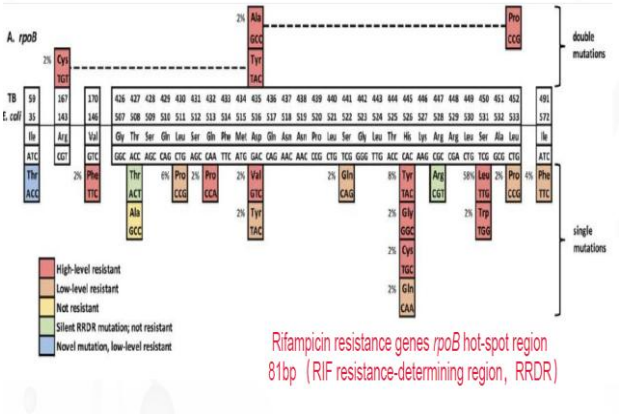
InaTB-Rif (Esora Medika Indonesia Inc., Indonesia) was a PCR-based machine designed to detect nucleic acid of MTB from sputum specimens with qualitative results. This was a closed system machine that included some processes of nucleic acid extraction, amplification and fluorescence signal detection. There were four channels in this machine: FAM, VIC, ROX, dan CY5. Dimension of this machine was 39 cm in length, 14 cm in width, and 36 cm in height, weighed about 7 kg, as shown in

Figure 1. A. Before nucleic acid extraction, the sample would be homogenized to improve the quality of the extraction process with an ultrasonic crusher (

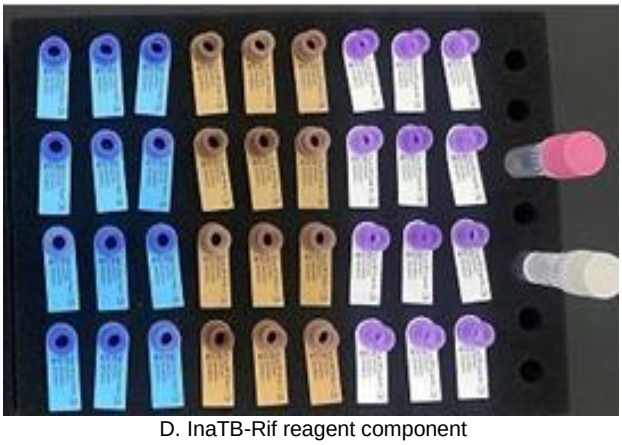
Figure 1. B.), using sonification. Before this, the sample was diluted in the tube, then inserted into this machine in a minute.

A. InaTB-Rif machine

B. *Ultrasonic Crusher*



C. RRDR region at gene *rpoB*



D. InaTB-Rif reagent component

Figure 1. Components of the InaTB-Rif machine: A) Nucleid acid extraction and amplification; B) Ultrasonic crusher; C) Region of mutation at gene *rpoB* for rifampicin resistance detection; D) InaTB-Rif reagent

This machine uses the InaTB-Rif reagent consists of genes *IS6110* and *IS1081,* to detect MTB and then identify rifampicin resistance using gen *rpoB* gene with amino acids 507 to 533. Studies showed 95% of *M. tuberculosis* mutations at segment 81 bp gen *rpoB* from codon 507-533, also known as Rifampicin *Resistance Determining Region* (RRDR), as shown in

Figure 1C. InaTB-Rif -RR reagent has 2 tubes; tube A detects MTB and tube B detects Rifampicin resistance as shown in

Figure 1D.

MTB detection is reported as positive or negative, and rifampicin resistance is reported as positive if rpoB mutations are detected, and negative if not. The MTB culture was performed using a liquid culture medium (BACTEC MGIT 960 Mycobacteria Culture System, BD Diagnostic Systems, Sparks, MD) following the manufacturer's guidelines, with incubation at 37°C for 2 to 6 weeks.

We analyzed our data using Stata v.17. Descriptive data were presented as means, standard deviations, and proportions. For diagnostic test, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), along with likelihood ratios (LR+ and LR-) of both Xpert MTB/RIF and InaTB-Rif, with MGIT culture as reference standard. We used a comparative receiver operating characteristic (ROC) curve to compare the area under the curve (AUC) of Xpert MTB/RIF and InaTB-Rif. We used the Kappa value to find out the agreement of rifampicin resistance detection between InaTB-Rif and Xpert MTB/RIF.

We evaluate the clinical applicability of both examinations by comparing turnaround time (TAT), cost per test and the applicability in a clinical setting compared with RT PCR regarding biosafety level requirements.

RESULTS

We recruited 78 subjects, then 20 subjects were excluded due to insufficient sputum quantity or quality for all three examinations, Xpert MTB/RIF assay, InaTB-Rif, or culture MTB. Three subjects were discharged due to culture errors, finally total number of subjects were 55.

Error! Reference source not found. p rovides a descriptive summary of the study subject. The mean age of the subjects was 46±16.0 years old, 61.8% of them were male. Regarding tuberculosis (TB) history, 36.4% of the subjects have a prior history of TB, while 63.6% do not. As for the acid-bacilli smear test, we found out that 45.4% of the subjects had positive results of TB, while 54.5% did not. Smoking behavior is reported in 27.8% of the participants, whereas 72.2% are non-smokers. As much as 70.9% of the subjects having no comorbid conditions. Among those with comorbidities, diabetes mellitus (DM) is the most common (12.7%), followed by HIV (3.6%), cardiovascular disease (1.8%), and hypertension (1.8%). Notably, 9.1% of the subjects have more than one comorbid condition. Lastly, the prevalence of type 2 diabetes mellitus (T2DM) specifically in the subjects is 21.8%, with the majority (78.2%) being non-diabetic.

Table 1. Characteristic of subjects

Variable	n (%)
Age (mean±SD)	46.0±16.0
Gender	
Male	34 (61.8%)
Female	21 (38.2%)
History of TB	
Yes	20 (36.4%)
No	35 (63.6%)
Smoking behaviour	
Yes	15 (27.8%)
No	39 (72.2%)
Acid-bacilli smear test	
Yes	25 (45.4%)
No	30 (54.5%)
Comorbidity	
None	39 (70.9%)
Diabetes mellitus	7 (12.7%)
Cardiovascular disease	1 (1.8%)
Hypertension	1 (1.8%)
Human immunodeficiency syndrome	1 (3.6%)
More than one comorbid	6 (9.1%)
Type 2 Diabetes mellitus	
Yes	12 (21.8%)
No	43 (78.2%)

Note: SD=standard deviation

MGIT cultures found 29 patients to be TB-positive and 26 patients to be TB-negative. The Xpert MTB/RIF identified 26 true positive cases, 5 false positive cases, 3 false negative cases, and 21 true negative cases, resulting in a total of 31 positive and 24 negative cases out of 55 samples tested by Xpert MTB/RIF. In comparison, the InaTB-Rif identified 27 true positive cases, 6 false positive cases, 2 false negative cases, and 20 true negative cases, with a total of 33 positive and 22 negative cases out of 55 samples tested by InaTB-Rif (Table 2). The results of crosstabulations suggest that both assays have a

high level of agreement with the MGIT culture, but with some variability in the number of false-positive and false-negative cases detected.

Table 2. Agreement of MTB detection among Xpert MTB/RIF, InaTB-Rif, and MGIT culture

Assays	MGIT culture		Total
	Positive	Negative	
Xpert MTB/RIF			
Positive	26	5	31
Negative	3	21	24
InaTB-Rif			
Positive	27	6	33
Negative	2	20	22
Total	29	26	55

With the results of crosstabulations, Table 3 provides the calculations of sensitivity, specificity, PPV, NPV, LR+, and LR- of both Xpert MTB/RIF and InaTB-Rif compared. The InaTB-Rif exhibits a slightly higher sensitivity (93.1%) compared to Xpert MTB/RIF (89.7%), indicating that it may be more effective at identifying TB-positive cases. However, Xpert MTB/RIF has a higher specificity (80.8%) than InaTB-Rif (76.9%), indicating a better ability to rule out non-TB cases.

Both assays demonstrate strong PPV and NPV, with Xpert MTB/Rif showing a slightly higher PPV (83.9%) compared to InaTB-Rif (81.8%). The LR+ and LR- values support the overall effectiveness of both assays, with Xpert MTB/Rif having a slightly higher LR+ (4.66) and a slightly lower LR- (0.128).

Table 3. Comparison of diagnostic accuracy between InaTB-RIF and Xpert MTB/RIF assay regarding culture MTB MGIT

Diagnostic accuracy	InaTB-Rif	Xpert MTB/RIF
Sensitivity (95% CI)	93.1% (0.77–0.99)	89.7% (70.2–0.97)
Specificity (95% CI)	76.9% (0.56–0.91)	80.8% (0.60–0.93)
PPV (95% CI)	81.8% (0.64–0.93)	83.9% (0.66–0.94)
NPV (95% CI)	90.9% (0.70–0.98)	87.5% (0.67–0.97)
LR+ (95% CI)	4.03 (1.99–8.20)	4.66 (2.10–10.30)
LR- (95% CI)	0.0897 (0.0232–0.347)	0.128 (0.043–0.380)

The ROC curve (Figure 2) indicates that both assays have a high area under the curve (AUC), with Xpert MTB/RIF showing an AUC of 0.8521 and InaTB-Rif closely following with an AUC of 0.8501. This finding suggests that both tests have good capabilities in distinguishing between patients with and without tuberculosis, with no significant difference in accuracy (*P*=0.965).

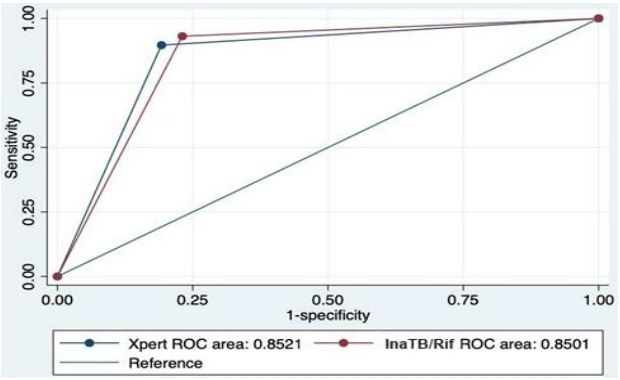


Figure 2. Comparison of AUC of InaTB-Rif (0.850) and Xpert MTB/RIF assay (0.852) with reference MGIT culture, *P*=0.965

Error! Reference source not found.4 p resents the agreement between the InaTB-Rif and Xpert MTB/RIF assays in detecting MTB and rifampicin resistance. For MTB detection, there is a strong agreement between the two assays, with 29 cases being positive by both methods and 20 cases being negative, as shown by a Kappa value of 0.776 (95% CI=0.555-0.997).

Table 4. Agreement of MTB and Rifampicin resistance detection among Ina-TB/Rif Rif and Xpert MTB/RIF assay

InaTB-Rif	Xpert MTB/RIF assay		Total	Kappa (95% CI)
	Positive	Negative		
MTB				
Positive	29	4	33	0.776 (0.55-0.99)
Negative	2	20	22	
Rifampicin resistance				
Positive	6	3	9	0.517 (0.21-0.82)
Negative	3	17	20	

In terms of rifampicin resistance detection, the agreement is moderate, with 6 cases identified as resistant by both assays, 17 cases identified as susceptible by both, but with some discrepancies leading to a lower kappa value of 0.517 (95% CI=0.212-0.821). The difference in kappa values suggests that while the two assays are in good concordance for MTB detection, there is less consistency in rifampicin resistance detection, which may reflect variations in the assays' sensitivity or specificity for detecting resistance mutations.

Regarding clinical applicability and cost effectiveness, InaTB-Rif and Xpert MTB/RIF have the same methods as a closed PCR test and test both *M. tuberculosis,* parallel with rifampicin susceptibility. The applicability was similar; both modalities only need biosafety level-1 grade settings, so they can be placed and conducted in primary

healthcare. The additional value of InaTB-Rif is in the running time, which is shorter by 50 minutes compared with Xpert MTB/RIF, 80 minutes and MTB RT-PCR 4 hours.

DISCUSSION

From 55 total patients that were included in this study, almost half the number of patients had negative MTB rapid molecular detection assays (Xpert MTB/RIF, InaTB-RIF, and culture). There are various reasons why a patient with suspected TB may test negative for *Mycobacterium tuberculosis*, including low bacterial load (early stage of TB or non-pulmonary TB), mixed infections involving Mycobacterium tuberculosis complex and non-tuberculous mycobacteria (NTM), inadequate sample collection (poor sample quality and timing of collection), and HIV co-infection (weakened immune system).[13,14]

This study reports the diagnostic capability of InaTB-Rif, a locally-developed rapid molecular test, in comparison with Xpert. We found that the diagnostic accuracy of InaTB-Rif is relatively comparable to Xpert, with a good level of agreement between both assays. The sensitivity of the assays observed in this study was 93.1% for InaTB-RIF and 89.7% for Xpert MTB/RIF. These figures are consistent with other studies, such as Ngangue *et al.*[15] which reported sensitivity rates of 91% for Truenat and 90% for Xpert MTB/RIF. However, the specificity observed in this study, ranging from 76% to 80%, is relatively lower than the specificity reported by Ngangue et al, who found specificity rates for Truenat and Xpert MTB/RIF to be between 96% and 99%.[15]

However, the lower specificity observed for InaTB-RIF compared to Xpert MTB/RIF indicates a higher rate positive results, but if we compare with culture result, number of true positive and true negative higher than Xpert MTB/RIF that lead into higher sensitivity, so among higher risk patients this may help reduce underdiagnosis, and we should also compare with other clinical result such as radiology and TB symptoms, to reduce false negative or misdiagnoses that lead into delay in treatment.

The strength of this diagnostic study lies in its direct comparison of the diagnostic performance of a locally developed molecular test, InaTB-RIF, with the well-established Xpert MTB/RIF assay. The study's robust design, including the use of a large sample size and the inclusion of a gold-standard reference (MGIT culture), strengthens the validity of the findings. Moreover, the study highlights the potential of InaTB-Rif as a viable alternative for tuberculosis diagnosis in settings where resources are limited, showcasing its comparable sensitivity to Xpert, which is crucial for early detection and treatment initiation. Additionally, the high level of agreement between InaTB-RIF and Xpert in detecting rifampicin resistance suggests that InaTB-RIF could be a valuable tool in managing drug-resistant TB cases, particularly in regions where Xpert's availability is limited.

If we examine more deeply the characteristics of these two diagnostic tools in terms of their capabilities when placed in primary health facilities with limited resources, InaTB-RIF has a shorter turnaround time (TAT) compared to Xpert MTB/RIF and conventional RT-PCR. While Xpert MTB/RIF and conventional RT-PCR require approximately 80 minutes and 4 hours, respectively, to deliver results, InaTB-RIF achieves this in about 50 minutes. This reduced turnaround time is particularly beneficial in high-volume testing settings, where faster results can significantly reduce patient waiting times and improve clinical decision-making processes

InaTB-Rif or Xpert MTB/RIF present practical diagnostic options compared to RT-PCR, particularly in resource-limited settings. InaTB-Rif operates efficiently in standard laboratory conditions with adequate airflow, eliminating the need for advanced biosafety cabinets (BSCs). Its simplified operation requires only basic training, reducing reliance on highly skilled personnel and enhancing accessibility in primary healthcare settings. In contrast, RT-PCR demands advanced training and stricter laboratory safety due to its manual and complex processes, making it less feasible for facilities with limited resources. Supported by the Indonesian

government's focus on fostering local innovations, InaTB-Rif holds significant potential to strengthen diagnostic capacity and reduce dependence on imported technologies.

In contrast, tools like Truenat, while promising, require multiple testing steps for MTB detection, followed by rifampicin resistance testing. This complexity increases the likelihood of errors, extends processing times, and raises costs. Moreover, Indonesia faces a growing burden of MDR-TB, accounting for more than 50% of resistant TB cases.[16] Tools like InaTB-RIF, which can simultaneously detect MTB and rifampicin resistance, provide a streamlined and more practical solution for addressing this urgent public health issue.

LIMITATION

The limitation of this study lies in the absence of rifampicin drug susceptibility testing (DST), and the validation was conducted in a single referral laboratory setting. To strengthen the evaluation of the assay's performance, future studies should include comparative analysis with phenotypic DST, whole-genome sequencing, and validation across multiple centers.

CONCLUSION

InaTB-Rif shows good sensitivity, specificity and AUC compared to MGIT culture as the reference standard for MTB detection. Ina-TB/Rif shows moderate agreement with Xpert MTB/RIF assay MTB in detecting Rifampicin resistance.

ACKNOWLEDGMENTS

The authors express their gratitude to Persahabatan Hospital as the site and core support and Epidemiology Indonesia for their help with data analysis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this work.

FUNDING

This research was supported by Esora Medika Indonesia Inc.. The funders had no role in designing the study, collecting and analyzing the data, or preparing the manuscript.

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