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Relationship Between Results of Genexpert RT-PCR and Erythrocyte Sedimentation Rate in Suspected Tuberculosis Patients

Tanti Listiyowati [1,2], Dita Pratiwi Kusuma Wardani [2*], Tantri Analisawati Sudarsono[2], Linda Wijayanti [3]
[1]BKPM Purwokerto, Indonesia
[2] Fakultas Ilmu Kesehatan, Universitas Muhammadiyah Purwokerto, Indonesia
[3]RSUD Banyumas, Indonesia
*Email : dita.tiwhie@gmail.com

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ABSTRACT
Pulmonary tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (MTB). The GeneXpert MTB/RIF is a diagnostic tool that can automatically detect the presence of MTB by molecular examination and can be used to detect MTB resistance to rifampicin. Erythrocyte Sedimentation Rate (ESR) was used to determine the rate at which erythrocytes settle in the blood. The ESR rate is related to inflammation caused by infection. This study aimed to determine the relationship between GeneXpert MTB/RIF results and ESR in suspected tuberculosis patients. This research uses a cross-sectional study. The sample used in this study were 56 new suspected TB patients who had never been treated for Anti-Tuberculosis Drugs (ATD) and underwent GeneXpert MTB/RIF examination. The sample was collected by purposive sampling with two result groups: Rif Sen and negative. The Chi-Square test (X^2) results show p-value = 0.000 and OR = 0.032. There is a significant relationship between GeneXpert MTB/RIF examination and ESR values in suspected tuberculosis.
Keywords*: GeneXpert; Erythrocyte Sedimentation Rate; Rif Sen; Tuberculosis*

ABSTRAK
Tuberkulosis (TB) paru merupakan penyakit infeksi yang disebabkan oleh bakteri *Mycobacterium tuberculosis* (MTB) dan menyerang organ paru-paru. Pemeriksaan GeneXpert MTB/RIF merupakan perkembangan alat diagnostik yang dapat mendeteksi adanya MTB secara otomatis dengan pemeriksaan molekuler dan dapat digunakan untuk mendeteksi resistensi MTB terhadap rifampisin. Laju Endap Darah (LED) merupakan pemeriksaan yang digunakan untuk menentukan kecepatan eritrosit yang mengendap dalam darah. Kecepatan laju endap darah berhubungan dengan inflamasi yang disebabkan adanya infeksi. Tujuan penelitian ini untuk mengetahui hubungan hasil GeneXpert MTB/RIF dengan LED pada suspek penderita Tuberkulosis. Penelitian ini menggunakan cross-sectional study. Sampel yang digunakan dalam

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penelitian ini sebanyak 56 orang pasien suspek Tuberkulosis baru yang belum pernah pengobatan Obat Anti Tuberkulosis (OAT) dan dilakukan pemeriksaan GeneXpert MTB/RIF. Pengambilan sampel dilakukan secara *purposive sampling* dengan 2 kelompok hasil pemeriksaan, yaitu: Rif Sen dan negatif. Hasil uji Chi-Square (X^2) menunjukkan p-value = 0,000 dan OR = 0,032. Terdapat hubungan signifikan antara hasil pemeriksaan GeneXpert MTB/RIF dengan nilai LED pada suspek penderita Tuberkulosis.
***Keywords**:* GeneXpert; Laju Endap Darah; Rif Sen; Tuberkulosis

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) and may cause death if left untreated. This disease occurred worldwide and was classified as the second biggest killer after Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS). TB causes inflammation of the lung parenchyma as much as 80%, while the other 20% attacks other organs. The most common TB transmission is through the respiratory tract by droplet infection, where MTB can enter the alveoli. Transmission occurs quickly when there is close contact with a patient with active pulmonary tuberculosis. Another form of transmission is through dust containing *M*TB (Laily, Rombot and Lampus, 2015; Hasnawati, 2018; Naim & Dewi, 2018).

World Health Organization (WHO) reported that the estimate for 2020 is 1,3 million TB deaths among HIV-negative people and an additional 214.000 among HIV-positive people. Deaths have increased compared to 2019 (WHO, 2021). There was an increase in TB cases in Indonesia in 2022 of 503,712 cases compared to 2021 of 443,235 cases (Kemenkes, 2022). The Case Notification Rate for TB in Central Java in 2021 was 110 per 100.000 population, and this number was increased to 2021 are 113 per 100.000 population. The Case Notification Rate in Banyumas District in 2021 is 198,9 per 100.000 population (DinkesProv Jateng, 2021).

WHO has recommended the GeneXpert MTB/RIF examination to diagnose pulmonary tuberculosis in adult patients (WHO, 2021). GeneXpert MTB/RIF is most widely used in routine analysis to confirm active TB cases and to detect mutations leading to rifampicin resistance (Kouassi *et al.*, 2016).

GeneXpert MTB/RIF is a diagnostic tool that can detect MTB automatically by molecular examination and is also used to detect MTB resistance to rifampicin. This

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rapid molecular test is automated and integrated through the Polymerase Chain Reaction (PCR) step based on the Deoxyribonucleic Acid (DNA) test to detect bacteria as well as detect the resistance of bacteria to rifampicin (Restrepo, 2018). Boehme *et al.* (2011) reported that the sensitivity and specificity of GeneXpert MTB/RIF for diagnosing pulmonary tuberculosis were 88% and 99%, while the sensitivity and specificity for detecting rifampicin resistance were 95% and 98%.

GeneXpert MTB/RIF can be used to diagnose TB because it has a high specificity and sensitivity value as a diagnostic tool and screening test for MTB and MTB resistance to rifampicin (Naim & Dewi, 2018). Erythrocyte sedimentation rate (ESR) determines the rate at which erythrocytes settle in the blood. Increased ESR values indicate the presence of acute inflammation (Nugraha & Badrawi, 2018). There is a relationship between MTB infection on the increased ESR value of pulmonary TB patients at the Makassar Community Lung Health Center (Hasnawati, 2018).

This research aimed to determine the relationship between the result of GeneXpert MTB/RIF and erythrocyte sedimentation rate in suspected tuberculosis patients in Purwokerto Community Lung Health Center.

METHOD

This research used a cross-sectional design conducted in June-July 2022 at Purwokerto Community Lung Health Center after obtaining ethical approval from KEPK Universitas Muhammadiyah Purwokerto No: KEPK/UMP/74/VI/2022.

A total of 56 suspected tuberculosis patients were included in this research using purposive sampling. The inclusion criteria were the subject who had registered as suspected pulmonary TB and underwent GeneXpert MTB/RIF, signed informed consent, aged 25-60 years, and never had Anti Tuberculosis Drug (ATD) treatment. The exclusion criteria were a suspected pulmonary TB who gave RIF Resistance (RIF Res) and RIF interdeterminant in GeneExpert MTB/RIF results or a subject with rheumatoid arthritis, anaemia, and pregnant women.

The medical record obtained the data of subject characteristics. The ESR value was obtained by Wester green Caretium XC A30 ESR Automatic tool and Sen/Negative RIF was obtained by GeneXpert MTB/RIF tool.

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The data were analyzed by Chi-Square (X2) test.

RESULTS AND DISCUSSION

Males were predominant in this research, that is 38 patients (67,9%). The suspected pulmonary TB patients with high ESR values were 40 (71,4%). The mean age was 44,7 ± 10,552 years old. The details of the subject characteristics are illustrated in Table 1.

Table 1. The Characteristics of the subject

No	Characteristics of subject	Frequency (n)	Percentage (%)	Mean ±SD	Median (Min-Max)
1	Age (y.o)	56	100	44,7 ± 10,552	45,50 (25-60)
2	Gender				
	Male	38	67,9		
	Female	18	32,1		
3	ESR value (mm/hours)				
	Normal	16	28,6	44,93 ± 32,911	33 (3-106)
	High	40	71,4		
4	Gene Expert Result				
	Rif Sen*	28	50		
	Negative*	28	50		

*) Rif Sen = RIF Sensitive, negative = Negative RIF

The predominant TB patients were male, as many as 78 (70,3%) in RSUP Sanglah Denpasar. Men smoke more often than women. Routine exposure to cigarette smoke accompanied by environmental pollution can damage the secretory process of the tracheobronchial mucosa and damage alveolar macrophages, allowing microorganisms such as MTB to easily penetrate the body's defense system in the lungs (Dewi, Andrika and Artana, 2020).

Males are less concerned about their health problems and are more prone to exposure with tuberculosis risk factors (Qo'imah *et al.*, 2022). They often consume alcohol and smoke, lowering their immune system and making them more susceptible to MTB exposure. In addition, males are more active outside the home and in contact with other people who are not yet known to be positive for pulmonary TB. Females are more aware of controlling diseases than males and do not transmit the disease (Rizqiya, Wuryaningsih and Deviantony, 2021).

In general, more TB patients are found at the age of <60 years because smokers are more likely to be found at a young age, so the

greater the risk of being infected with TB (Dewi, Andrika and Artana, 2020). Age 15-50 is a productive age and vulnerable to TB because of the high activity and interaction with others (Dina, Zaini and Yahya, 2019).

An increase in the ESR value in TB patients can occur because MTB infects the alveoli, which causes inflammation resulting in an increase in plasma viscosity and an increase in fibrinogen (Hidriyah, Rahmita and Trisna, 2018). The presence of inflammation causes the release of acute mass proteins, causing rouleaux erythrocytes accompanied by an increase in erythrocyte velocity, increasing ESR. In addition, several factors such as tools, temperature, place, and ESR detection techniques also contribute to increasing ESR (Kasih & Sulastina, 2019). A Chi-Square (X^2) relationship test between GeneXpert MTB/RIF results and ESR value was illustrated in Table 2.

Table 2. Relationship Between GeneXpert MTB/RIF Results and ESR in Suspected Tuberculosis Patients.

Gene Expert	ESR Values		P-value	OR	CI
	Normal	High			
Rif Sen	1 (3,6%)	27 (96,4%)	0,000	0,032	0,004–0,270
Negative	15 (53,6%)	13 (46,4%)			

The GeneXpert MTB/RIF test is a molecular detection method based on nested real-time PCR to detect complex MTB DNA qualitatively, quickly, and accurately. This method allows MTB that is not found on the microscopic test but can still be detected on the GeneXpert MTB/RIF test because this method can detect MTB in crushed form (Utami *et al.*, 2021). The GeneXpert MTB/RIF method has high sensitivity and is used as a screening tool for pulmonary TB patients. In contrast, a high specificity value can determine if a patient is genuinely confirmed with TB or vice versa. This method can also be used as a determinant for diagnosing pulmonary TB so that therapy can be given immediately (Permatasari *et al.*, 2021). The factor affecting false positives in GeneXpert MTB/RIF test is not yet fully known, so clinicians cannot determine whether or not a positive GeneXpert result following well-treated pulmonary (Costantini, Marando and Gianella, 2020).

Table 2 shows that 27 (96,4%) suspected TB patients with GeneXpert Rif Sen results had high ESR, while 15 (53,6%) suspected TB patients with negative GeneXpert results had normal ESR. There is a relationship

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between GeneXpert MTB/RIF Results and ESR in suspected TB Patients (p= 0.000, OR= 0.032).

The ESR test determines the speed of erythrocytes in the blood fall to the bottom of a vertical tube within a certain time, measuring the distance from the top of the erythrocyte column that settles up to the fluid limit in a certain period of determining the sedimentation rate (Naim, 2019). ESR is a non-specific measure of inflammation. Several non-inflammatory conditions that can cause increasing ESR include anemia, kidney failure, obesity, aging, female sex, and woman during menstruation and pregnancy. Autoimmune disorders, infection, and some cancers also contribute increasing of ESR. Previous research found a non-specific clinical significance of ESR in routine TB evaluation (Sorsa, 2020). ESR values are within normal limits in minor local infectious diseases, such as acute disease in the infectious phase of mucous membranes, with little inflammatory reaction (Hasnawati, 2018).

Active TB is generally associated with very high ESR values (≥ 100 mm/hour) and with a marked increase in all sputum values of smear-positive patients (Sulochana *et al.*, 2022). ESR and *C Reactive Protein* (CRP) increase in most patients with active TB. The levels of ESR can be helpful indices to determine the extent of the disease. ESR can react to several acute conditions in the body, such as infection, burns, surgery, or trauma (Alamlih *et al.*, 2020).

The GeneXpert MTB/RIF is more sensitive and specific than ESR because it can detect MTB and rifampicin resistance by detecting the rpo gene and its mutation associated with rifampicin resistance using PCR technique (Sasikumar *et al.*, 2020; Solanki *et al.*, 2020). This method has a cumulative sensitivity of 90.2%, providing results within 2 hours, and permits quick identification of strains resistant to rifampicin because it has specificity until 99% (Costantini, Marando and Gianella, 2020).

Another method for MTB detection, for example, Acid Fast Bacilli (AFB) culture testing, needs better sensitivity and specificity than GeneExpert MTB/RIF. As the consequences of the higher cost of the GeneExpert MTB/RIF test, it is essential to decrease the chance of getting failed or invalid test results (Elbrolosy *et al.*, 2021).

The ESR test is irreplaceable to the GeneXpert MTB/RIF as a molecular diagnosis of pulmonary TB. We need

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histopathology results as a confirmative test, and also AFB culture remains the gold standard to justify the diagnosis of TB (Solanki *et al.*, 2020).

CONCLUSION

There was a significant relationship between GeneXpert MTB/RIF results and ESR values in suspected TB patients (p = 0,000, OR= 0,032). It is necessary to confirm with histopathology test and AFB culture test to evaluate the role of ESR as an inflammatory marker in TB patients.

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