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Expression of mIRNA-142-3P in Peripheral Blood From Active and Latent Pulmonary Tuberculosis

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ABSTRACT

This study aimed to asses miRNA-142-3p expression of active and latent pulmonary tuberculosis. 33 people with active Tuberculosis (TB), 36 household contacts who tested positive for IFN-released assay (IGRA), and 39 healthy controls made up this case-control study. Latent pulmonary tuberculosis infection in household contacts was identified using an IGRA based on an enzyme-linked immunosorbent test. miRNA-142-3p expression was measured by quantitative real-time PCR. Data analysis used analysed of variance and receiver operating characteristic (ROC) curves. The results showed that miRNA-142-3p expression differed significantly between active TB, latent TB and healthy participans (control p=<0.001). ROC curve analysis showed that miRNA-142-3p expression had 66.7% sensitivity and 61.5% specificity with an area under the ROC curve (AUC) of 0.725 (95% confidence interval (CI): 0.606 – 0.844) in active TB. The miRNA-142-3p ROC curve had 63.9% sensitivity and 51.3% specificity with an area under the ROC curve (AUC) of 0.603 (95% confidence interval (CI): 0.475 - 0.730) for laten TB. miRNA-142-3p expression was increased in patients with active pulmonary TB. Therefore, miRNA-142-3p represents a potential biomarker active pulmonary TB but not to latent TB.

Keywords: *Tuberculosis, Pulmonary, Peripheral Blood, Mycobacterial Infections.*

1. INTRODUCTION

Globally, tuberculosis (TB) causes a high rate of mortality and morbidity. In 2022, an estimated 9.6 million people will develop TB, and 1.5 million people will die from TB, according to to global TB report in 2022 [1]. To restrict the spread of TB and to treat mycobacterial infections with antibiotics, the initial detection of TB infection is necessary. The typical procedure required growing microorganisms in a selective medium for a period of 3 to 12 weeks [2]. Low sensitivity exists when creating a smear from sputum, and while PCR and immunological tests are quick diagnostic methods, they are unreliable due to the possibility of false positive and negative results [3,4].

A major worldwide health concern, TB persists despite advances in pulmonary medicine. Bacillus Calmette-Guerin (BCG) is the only vaccination now in use; nevertheless, this vaccine loses potency after ten years or so [5]. The typical clinical approach for diagnosing TB and latent TB is to use the interferon-gamma release assays (IGRA), which is thought to be a more sensitive test since it quantifies the amount of interferon-gamma (IFN-γ) released by blood cells in reaction to particular Mtb antigens [6]. The tuberculin skin test (TST) is similarly used in this regard. Still, false positive results are frequently obtained with these procedures. Preventing TB involves several challenges, including the development of a sensitive and effective method for detecting latent TB and a knowledge of the disease biology. Therefore, there is an increasing need for new biomarker or new diagnostic method for TB diagnosis. Recently, microRNA (miRNA) have been introduced a new

diagnostic biomarkers that are widely involved in several cases such as cancer heart disease, pregnancy, immune and many infection diseases [5].

MicroRNAs may be used as biomarkers for active tuberculosis, according to more recent research. The expression of genes involved in development, cell differentiation, proliferation, and apoptosis is modulated by microRNAs (miRNAs), which are tiny, noncoding, single-stranded RNAs. According to estimates, microRNAs target up to 20% of all human transcripts. Since these small RNA molecules actively circulate in body fluids and have been shown to be more stable than messenger RNAs, it is believed that they serve as a more direct signal of altered physiology. MicroRNAs have in fact been the subject of much research about their therapeutic and diagnostic potentials, particularly in the field of cancer research [6].

Many studies have shown the alteration of miRNAs expression profiles in clinical samples (sputum, serum, pleural effusion, PBMC) in patients with active TB. The studies employing microarray technology have discovered miRNAs as candidate TB biomarkers [7–10]. Study kleinsteuber et al, who compared the expression of 29 miRNAs in $CD4^+$ T cells from peripheral blood, who showed that lower expression of miR-21, miR-26a, miR-29a, and miR-142-3p in $CD4^+$ T cells from children with tuberculosis as compared to healthy children with latent TB. we detected markedly lower expression of miR-26a (P,0.01), miR-29a (P,0.01), and miR-142-3p (P=0.05) [11].

The diagnosis of latent TB infection can also be hard, due to the limitations of current techniques – the tuberculin skin test and interferon-gamma release assays. In this regard, a number of miRNA signatures that differentiate between latent and active tuberculosis have been found [12–14] . Lyu et al. detected unique sets of serum miRNAs for both latent TB (hsa-let-7e-5p, hsa-let-7d-5p, hsa-miR- 450a-5p and hsa-miR-140-5p) and active TB (hsa-miR-1246, hsa- miR-2110, hsa-miR-370-3P, hsa-miR-28-3p and hsa-miR-193b- 5p (Lyu, 2019). Interestingly, utilizing the expression profile of eight distinct miRNAs (hsa-miR-122-5p, miR-151a-3p, miR-451a, miR-486-5p, hsa-let-7i-5p, miR-148a-3p, miR-21-5p, and miR-423-5p) latent TB could be identified from active illness with an accuracy of 71.8% [14]. Another study, Wu et al. demonstrated that Profiling of microRNA and gene expression was performed to identify differentially expressed transcripts among 7 healthy control, 7 active TB, and 7 LTBI individuals. they founded the level of hsa-miR-142-3p and hsa-miR-21-5p expression to be enhanced in LTBI relative to TB, and hsa-let-7i-5p expression, increased in TB compared with healthy controls[6].

In this study, we evaluated miRNA-143-3p as a potential biomarker for early detection of latent and active tuberculosis, which may have stopped the spread of tuberculosis.

2. MATERIAL AND METHOD

2.1 Study design and subjects

Cross sectional study. Patients with pulmonary TB diagnosed at the Makassar Community Lungs Health facility, a referral facility for TB cases from primary health care in Makassar, Indonesia, and those with household contact made up the population of this study.

2.2 Sample Collection

The samples used in this research were sputum and blood taken from the population of tuberculosis sufferers, and blood samples for household contacts and healthy controls. The research was conducted at Hasanuddin University Medical Research Laboratory (HUM-RL) using 33 samples of active TB patients, 36 latent TB patients and 39 control samples. Bacteriologically confirmed pulmonary tuberculosis sufferers show symptoms of active TB, are patients with new cases of TB, sputum examination with acid-fast bacillus smear shows positive results, GeneXpert molecular rapid test examination is positive. Chest x-ray examination shows an infiltrate There were 60 samples of latent TB sufferers, IGRA examination was carried out with 36 positive results and 39 samples were normal controls with negative IGRA results.

2.3 Sample Processing and assesment

2.3.1 Sputum Collection

A study subject is interviewed utilizing a set of guidelines. The study subject's sputum was collected in order to do the Zielh-Nielsen staining procedures and geneExpert (rapid moleculer test)

2.3.2 Blood Collection

5 – 10 ml venous blood samples were obtained household contacts and patients with active pulmonary tuberculosis gave blood samples in a QuantiFERON-TB Gold (QFT-Plus) In-Tube from Qiagen GmbH, Qiagen Strasse 1, 40724 Hilden, Germany. To extract total RNA, blood samples were centrifuged at 3000 rpm.

2.3.3 Total RNA Extraction

Total RNA was extracted and purified from blood sample using the Q/Aamp TNA blood mini kit (Qiagen, USA, Cat No.52304), according to the manufacturer's instructions.

2.3.4 Complementary DNA (c DNA) synthesis

Reverse transcription polymerase chain reaction (PCR) was used to create cDNA from extracted RNA. The iScript cDNA Synthetic Kit (Bio-Rad; Hercules, CA, USA) was used for this procedure in accordance with the manufacturer's guidelines. Real-time PCR (q-PCR) was used to quantify the cDNA.

2.3.5 Quantification of miRNA-143-3p with real-time quantitativ PCR (qPCR)

Using q-PCR and spesific primers, we measured the expression of miRNA-142-3p. Basic principle of this method is that only the specific miRNA-142-3p sequence in the cDNA will be amplified by the spesific primer pair. A commercial kit (miRCURY LNA miRNA PCR test GeneGlobe ID YP00204291 Qiagen -Cat No: 20901410-2 utilized for miRNA-142-3p) was used for the amplification process. The precise miRNA-142-3p primer sequence was 5'UGUAGUGUUUCCUACUUUAUGGA. The number of amplification cycles that passed before the amplicon exceeded the detection threshold is the cycle threshold, which is given as the amplification result that was observed in real-time.

2.4 Analisa statistic

Analysis of variance (ANOVA) was used to examine the expression of miRNA-142-3p in the groups of people with active pulmonary TB, latent pulmonary TB, and healthy controls. The data were analyzed using SPSS statistic v 23.0 (IBM Co; Armonk, NY, USA). This study also employed the curve ROC analysis to describe diagnostic accuracy. All findings with p 0.05 or higher were regarded as statistically significant.

3. RESULT

3.1 Patient characteristic

Patient characteristics included age, sex, and relationship to active TB patients. Of the 33 patients with active pulmonary tuberculosis, as indicated in Table 1, 23 were men and 10 were women. Fifteen men and twenty-one women were among the household contacts in the latent pulmonary TB groups with positive IGRA results. Twelve men and twenty-seven women made comprised the household contacts in the healthy control group who had negative IGRA results or were otherwise in good health. According to the IGRA results, there is a significant correlation (p=0.003) between sex and the incidence of latent TB, active TB, and healthy controls. Age-wise, the sample was homogeneous (0.150).

Table 1. Study participans characteristic in the active TB, latent TB and healthy control

Characteristic	**group**			***p-value***
	Active TB (n=33)	**Latent TB (n=36)**	**Healthy controls (n=39)**	
Age (year)	37.45±13.94	37.14±12.01	39.97±15.12	0.803
Age (categori)				
<26	10 (30.3)	8 (22.2)	11 (28.2)	0.150
26-39	8 (24.2)	11 (30.6)	8 (20.5)	
40-50	8 (24.2)	12 (33.3)	5 (12.8)	
>50	7 (21.2)	5 (13.9)	15 (38.5)	
Sex				*0.003*
Female	10 (30.3)	21 (58.3)	27 (69.2)	
Male	23 (69.7)	15 (41.7)	12 (30.8)	
Relationship				0.070
Parents		6 (16.7)	3 (7.7)	
Children		8 (22.2)	8 (20.5)	
Spouse (Husband/wife)		13 (36.1)	17 (43.6)	

Sibling	7 (19.4)	2 (5.1)
Other	2 (5.6)	9 (23.1)

3.2 miRNA-142-3p Expression in Active TB, Latent TB and Healthy Participants

The average q-PCR-based miRNA-142-3p expression was 21.32 in the latent TB group and 8.69 in the active TB groups and 0.83 in the healthy control (fig.1). A statistical analysis using the ANOVA test showed that miRNA-142-3p expression was significantly higher in active TB than in the latent TB and healthy control groups ($p<0.001$; table 2). The difference in miRNA-142-3p expression was only significant between active TB groups and the healthy control (p-value=0.009). There was no difference in expression between the active TB group and laten TB (p=0.043) as well as laten TB with healthy control (p=0.747) (p-value > 0.05).

Table 2. The miRNA-142-3p expression level in active TB. Latent TB, and healthy control groups

Groups	N	Mean	SD	SE	Expression 95% Cl Low	Expression 95% Cl High	p-value
Healthy control	39	0.7561	1.47061	0.23549	0.2794	1.2328	0.001
Latent TB	36	1.0013	1.44236	0.24039	0.5132	1.4893	
Active TB	33	2.0467	2.00257	0.34860	1.3366	2.7568	

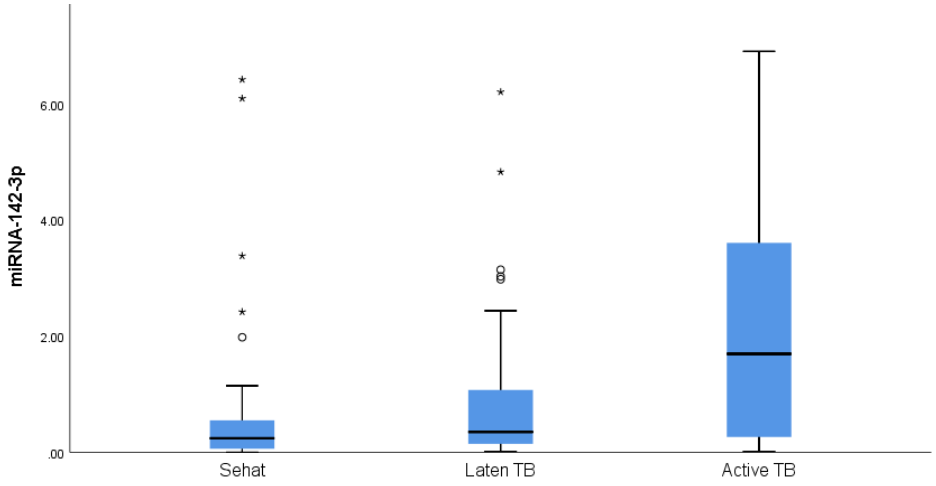

Figure 1. miRNA-142-3p expression in the active TB, laten TB and healthy control groups. Difference in miRNA-142-3p expression between groups were

3.3 The Receiver Operating characteristic (ROC) curve analysis

The potential of miRNA-142-3p as a sensitive biomarker for active pulmonary tuberculosis infection is demonstrated by a ROC curve (Fig. 2) with p value 0.001

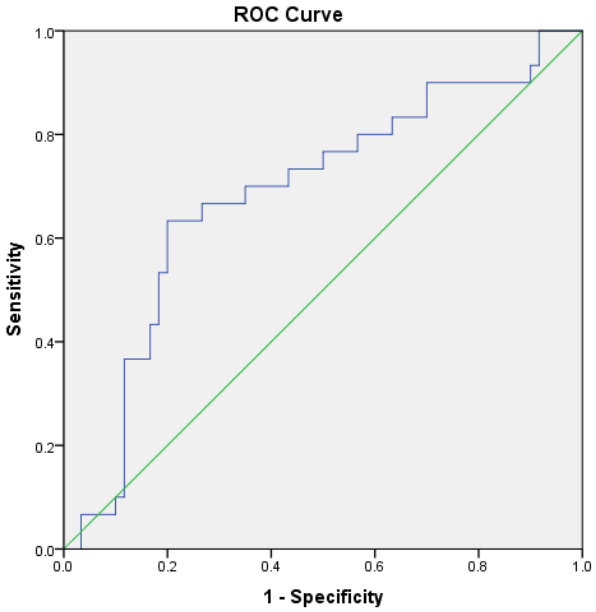

Figure 2. miRNA-142-3p expression as a potential biomarker of active TB (p <0.05)

The AUC is 0.725 (95% confidence interval ¯CI: 0.606 – 0.844) and the sensitivity and specificity are 66.7% and 61.5%), respectively. Additionally, table 2 shows a significant correlation (p<0.001) between miRNA-142-3p expression and active pulmonary tuberculosis.

Additionally, a ROC curve (fig. 3) with a p value 0.127 and 63.9% sensitivity, 51.3% specificity, and an area under the ROC curve (AUC) of 0.603 (95% confidence interval (CI: 0.475 – 0.730) demonstrates of miRNA-142-3p expression of latent pulmonary TB infection. Additionally, there was significant correlation (p<0.001) between miRNA-142-3p expression and latent pulmonary tuberculosis.

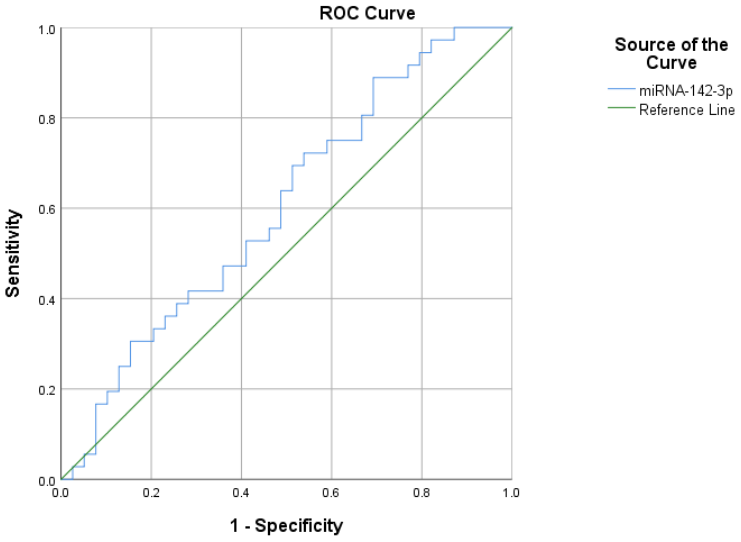

Figure 3. miRNA-142-3p expression of latent TB (p=0.082)

4. DISCUSSION

MiRNA is a form of single-stranded RNA molecule that ranges in length from 18 to 25 nucleotides. Its purpose is to restrict the activity of the genes it targets later in the transcriptional process. The RNA known as miRNA is not involved in protein coding. Instead, the messenger RNA (mRNA) of the target gene interacts with its final transcript. The function of miRNA is to control mRNA translation in concert with other regulatory elements, such as transcription factors. In areas of the genome

that were previously thought to be non-coding, miRNA are mostly found. The miRNAs are estimated to be encoded by 2%–5% of human genes across the genome. Polycistronic transcripts frequently carry miRNAs encoded therein. Due to the possibility of a single miRNA having several target mRNAs, it is believed that miRNAs regulate almost one-third of all human genes [15,16]

MiRNAs are commonly regarded as non-invasive indicators of health and prognosis. A multitude of studies have employed miRNA as a diagnostic biomarker for the early diagnosis of many cancers, including colorectal cancer, lung cancer [17,18] and breast cancer [19]. In light of the recent discoveries about miRNAs and the knowledge that miRNAs are stable in serum [20]. They can therefore be regarded as a reliable biomarker[21,22]. The diagnosis of tuberculosis infection is more serious than that of many other bacterial infections [23]. Early detection of the illness is one of the most efficient ways to stop the spread of tuberculosis. MiRNAs can be trustworthy as potential diagnostic biomarkers because many diagnostic techniques nowadays are unable to differentiate between active TB and latent TB[24].

The human host has an enormous killing machinery, like phagocytosis, apoptosis, and autophagy, and so on, for the invading pathogen. On the other hand, the intracellular *Mycobacterium tuberculosis* (MTB) uses a variety of techniques to get around the host resistance. Mycobacterium's miRNA-based modulatory responses are clarified by the current transcriptome method. The miRNAs produced by Mycobacterium decrease the phagocytic function of macrophages at different stages [25]. MiR-142-3p affects the bacterial contact and ingest via N-wasp. Upregulated miR-142-3p in J774A adversely regulated N-wasp, an action-binding protein crucial to actin dynamics in the phagocytosis process. During an MTB infection, one cell line and primary human macrophages [26].

Autophagy is the process by which cells maintain cellular environmental homeostasis. What's more, the autophagy in macrophages contributes to elimination of intracellular bacterium like MTB. Once the level of autophagy is altered, the survival rate of MTB also changes. Numerous studies show that miRNAs regulate MTB survival by finetune autophagy through multiple ways [27], demonstrated that miR-142-3p adjusted autophagy by targeting 3′-UTR of ATG16L1 and ATG4c, thus made impact on *M. tuberculosis* H37Ra within macrophages. Given that miR-142-3p regulated autophagy via ATG16L1 and ATG4c, these data suggested miR-142-3p might be a new autophagy-related biomarker and a potential target for clearance of intracellular bacterium [27]. It was also reported that M. bovis BCG-mediates downregulation of miR-142-3p which targets IRAK-1 and plays a critical role in the regulation of innate immune response through transfer signaling from TLR. Decreased expression of miR-142-3p results in a subsequent increase in production of NF-κB, TNF-α and IL-6 in the macrophages [28].

This study examined 36 household contacts with positive Elisa-based IGRA results in the latent TB group and 39 individuals with negative IGRA results in the healthy control groups. According to the patient characteristic, there were three patient groups with active pulmonary TB: those with positive IGRA household contacts, those with negative IGRA household contacts, and healthy controls ($p < 0.001$). the result similar to World Health Organization data showing that more males than females are diagnosed with smear-positive TB [1].

This study examined miRNA-142-3p expression in active TB, latent TB and healthy control groups using qPCR. Its result showed that miRNA expression was (CI: 0.235– 4.257) in active group and in the latent group (CI: 0.152– 0.732) (fig.1) when we compared the active TB and healthy control groups to the laten TB group, miRNA-142-3p level were considerably significantly in the active TB group based on ANOVA test.

This result consisten with finding with those of RothChild et al, MTB infected mouse, who 4 upregulated (miR-24, miR-142, miR-155, and miR-212) and 3 downregulated (miR-19a, miR-202, and miR-376a) in response to Mtb infection relative to uninfected controls (Benjamini– Hochberg corrected P value ≤ 0.05 and fold-change [29]

Study kleinsteuber et al, who compared the expression of 29 miRNAs in CD4+ T cells from peripheral blood of tuberculosis patients, latent TB, and non infected control donors (PPDneg), who showed that lower expression of miR-21, miR-26a, miR-29a, and miR-142-3p in CD4+ T cells from children with tuberculosis as compared to healthy children with latent TB. [11].

Similarly, Study Gao et al 2021, There were differential expression of miR-30c and miR-142-3p between TB patients and healthy control ($p < 0.05$), relatively less expression of miR-142-3p (OR: 0.43, 95% CI: 0.205– 0.900) were associated with tuberculosis between TB patients and healthy control [30].

Our ROC curve analysis using cut-off 0.01 showed that miRNA-142-3p expression has the potensial to act as a biomarker of active pulmonary tuberculosis infection, with 66,7% sensitivity, 61.5% specificity and an AUC of 0.725 (95% CI:0.606 – 0.844). moreover, miRNA-142-3p expression correlated significantly with active pulmonary TB (fig. 1). In addiction, miRNA-142-3p showed 63.9% sensitivity, 51.7% specificity, and AUC of 0.603 (95% CI:0.475 – 0.730) for latent TB infection. moreover, miRNA-142-3p expression was no significantly correlatin with latent TB.

These procedures, however, are not without difficulties. The primary issue in this situation is the detected miRNAs' low diagnostic specificity and lack of repeatability. The published miRNA signatures lack consistency despite a significant number of investigations [31]. These variations could result from different sample sources, such as serum or plasma [32].

Numerous studies have demonstrated that blood miRNAs can originate from various organs in both healthy individuals and sick, and that the expression profiles of miRNAs in venous and arterial plasma differ from those in tissues [33]. Moreover, the expression of circulating miRNAs is influenced by the age of the patients and the existence of numerous comorbidities [32]. Furthermore, inconsistent results may arise from the sampling strategy, which includes sample preservation and processing [34]. For this reason, protocol uniformity must be created. Individual miRNA has a limited diagnostic value for TB, when integrated miR-142-3p and add some another mirna to develop two models for the diagnosis of tuberculosis, diagnostic performance has been both significantly improved[35,36,37,38].

The limitations of this study are, firstly, for latent TB, the clinical information through questionnaires is subjective and laboratory tests and GeneXpert molecular rapid test tests were not carried out to rule out active TB. Second, it does not check the severity of active TB disease so this can influence the research results.

5. CONCLUSION

The expression of miRNA-142-3p was elevated in patients with both latent and active pulmonary TB. Furthermore, compared to latent TB and healthy groups, active TB group showed higher expression of miRNA-142-3p. It is also possible to use miRNA-142-3p as a potential biomarker to diagnose active tuberculosis but not latent tuberculosis.

6. DISCLOSURES

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No funding or sponsorship.

ETHICAL APPROVAL

All procedure for human experiment has been approved by our institutional review board.

CONSENT

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their prospective data base and files for research work.

AUTHOR CONTRIBUTION

Nur Afiah, Uleng Bahrun, Muhammad Nasrum Massi, Irawaty Djaharuddin, Lahammad Abdullah initiated and designed the study. Ilhamjaya Patellongi performed the statistical analysis. Agussalim Buchari, Harun Iskandar contributed in the data processing. All authors have read and approved the final manuscript.

PROVENANCE AND PEER REVIEW

Not commissioned, externally peer-reviewed.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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