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ORIGINAL ARTICLE

Diagnostic Predictors of MDR-TB Using Biomarkers sCD14, PGLYRP2, and FGα in Populations with and without Diabetes Mellitus

Elne Vieke Rambi[1*], Marjes Netro Tumurang[1], Dionysius Sumenge[1], Michael Vallery Loueis Tumbol[1]

[1]*Department of Medical Laboratory Engineering, Poltekkes Kemenkes Manado, Manado, North Sulawesi, Indonesia*
Correspondence: *viekerambi@yahoo.com*
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ABSTRACT

OBJECTIVE: To analyze differences in biomarkers (sCD14, PGLYRP2, and FGα) as diagnostic predictors of MDR-TB with and without diabetes mellitus comorbidity in Manado, Indonesia.

METHODOLOGY: A cross-sectional study was conducted from February to December 2025 at Prof. Dr. RD Kandou General Hospital and a community health center. A total of 180 respondents were divided into three groups: TB-DM (n=45), MDR-TB (n=45), and healthy controls (n=90). MDR-TB diagnosis was confirmed via Gene Xpert MTB/RIF and/or drug sensitivity testing, while TB-DM included pulmonary tuberculosis patients with comorbid diabetes mellitus. Biomarker levels were measured using a sandwich ELISA. Statistical analysis employed one-way ANOVA (α=0.05) with Levene's test for homogeneity, using SPSS version 25.0.

RESULTS: Variances were homogeneous across all biomarkers ($p>0.05$). sCD14 levels differed significantly between groups ($F=3.112$; $p=0.035$), with MDR-TB at 102.89±29.45 ng/mL, TB-DM at 77.42±42.31 ng/mL, and controls at 108.52±14.23 ng/mL. PGLYRP2 demonstrated the strongest intergroup difference ($F=14.496$; $p<0.001$), showing a consistent gradient: MDR-TB (5.12±1.08 ng/mL), controls (4.21±1.12 ng/mL), and TB-DM (2.73±0.52 ng/mL). FGα showed no significant difference ($F=0.999$; $p=0.377$).

CONCLUSION: PGLYRP2 emerged as the most promising biomarker for differentiating MDR-TB from other groups, exhibiting a clear gradient pattern. sCD14 demonstrated significant heterogeneity, particularly in TB-DM, suggesting its potential relevance in comorbid conditions. FGα showed no discriminatory value across the studied groups.

KEYWORDS: Multidrug-Resistant Tuberculosis (MDR-TB), Serum Biomarkers, Diabetes Mellitus, Diagnostic Predictors

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is one of the most real and worrying threats worldwide. MDR-TB is TB caused by Mycobacterium tuberculosis that is resistant to at least isoniazid and rifampin. Isoniazid and rifampin are the two most effective drugs in treating TB [1]. Diabetes mellitus comorbidity further complicates the detection of MDR-TB. Comorbidity is a risk factor for the development of TB drug resistance. Previous research has shown that soluble CD14 (sCD14) is an inflammatory biomarker that significantly influences insulin resistance and diabetes [2].

Indonesia has one of the highest TB prevalence rates worldwide, both in multidrug-resistant TB (MDR-TB) and in cases of diabetes mellitus (DM). This is often attributed to lifestyle factors. Previous research has shown that serum biomarkers are a good diagnostic tool for detecting TB [3]. Previous research has shown that access to molecular testing is often a barrier to diagnosing MDR-TB. This is what a serum biomarker-based approach offers for early detection, thus avoiding the risk of death from TB, whether with comorbidities or MDR-TB. The use of Pentraxin-3 for diabetic nephropathy is known to be a potential biomarker for detecting TB in diabetes [4].

Previous research has shown that sCD14 has greater sensitivity and specificity than other biomarkers [5]. It is also known that FGA can play an important role in inflammation and coagulation processes, making it a marker of pathological conditions [6]. Serum proteins can be biomarkers of TB [7]. Clinical applications require biomarkers that have been tested to minimise errors in the field and in community applications[8,9].

Soluble CD14 (sCD14), peptidoglycan recognition protein 2 (PGLYRP2), and fibrinogen alpha chain (FGA) are three serum proteins whose mechanistic roles in tuberculosis (TB) pathogenesis position them as promising biomarkers for multidrug-resistant TB (MDR-TB). sCD14 is a monocyte-macrophage activation marker; during early TB infection, monocytes migrate to the infection site and differentiate into macrophages, triggering immune responses, and its decreased abundance in MDR-TB relative to drug-sensitive TB (DS-TB) likely reflects diminished monocyte activation [10–12]. PGLYRP2 is an N-acetylmuramyl-L-alanine amidase that hydrolyzes bacterial peptidoglycan, functioning in innate immune defense by digesting biologically active peptidoglycan into inactive fragments; its marked upregulation in MDR-TB compared to DS-TB reflects a heightened innate immune defense response against resistant mycobacteria [13–15]. FGA, a coagulation factor component, is elevated in TB patients, particularly in MDR-TB, indicating that the hypercoagulable and inflammatory state accompanying severe TB infection can be captured through fibrinogen levels, thereby serving as an indicator of disease severity [13–15].

This study is unique of simultaneously evaluating all three biomarkers in a specific population, such as Manado Province, with DM-TB and MDR-TB as the study groups. This approach differs from most studies, which generally evaluate biomarkers individually. This study aims to analyze the potential of serum biomarkers sCD14, PGLYRP2, and FGA as diagnostic predictors of MDR-TB, with the hope of providing concrete evidence for the development of effective TB detection and diagnostics.

METHODOLOGY

A cross-sectional design was used in the study conducted at Prof. Dr RD Kandou Manado General Hospital (a referral hospital for MDR-TB patients) and at community health centres in Manado city (referral hospitals for TB with DM comorbidity). The data and specimens obtained were analyzed at the Laboratory of the Department of Medical Laboratory Technology, Faculty of Health Sciences, Poltekkes Kemenkes Manado. The research was conducted from February to December 2025.

The population in this study consisted of three groups: TB patients with MDR-TB based on GeneXpert MTB/RIF and/or drug-sensitivity testing (DST), TB patients with pulmonary TB comorbid with diabetes mellitus, and healthy individuals as a control group. The total population based on the above criteria was 117, of which 117 were classified into the TB DM and MDR-TB groups. The number of samples was calculated using the Slovin formula, with an error rate (e) of 0.05. Based on the calculation $n = N/(1 + Ne^2)$, $n = 117/(1 + 117 \times 0.0025) = 117/1.2925 = 90.5$. so that the number of subjects in the MDR-TB group was 45, in the TB-DM group was 45, and in the negative control group (healthy/normal) was 90.

Inclusion criteria for the MDR-TB group included tuberculosis patients diagnosed with MDR-TB based on Gene Xpert MTB/RIF testing and/or drug sensitivity testing (DST). For the TB-DM group, inclusion criteria included patients with pulmonary tuberculosis who had comorbid diabetes mellitus. Meanwhile, the control group consisted of healthy individuals with no history of tuberculosis or diabetes mellitus.

Three independent variables were used in this study, including serum soluble CD14 (sCD14), Peptidoglycan Recognition Protein 2 (PGLYRP2), and Fibrinogen Alpha Chain (FGA). These three biomarkers were measured in nanograms per milliliter (ng/mL). The dependent variables in this study were also divided into three groups: patients with tuberculosis and multiple drug resistance (MDR-TB), patients with tuberculosis and comorbid diabetes mellitus (TB with DM), and negative controls consisting of healthy individuals without a history of tuberculosis or diabetes mellitus.

Four instruments were used for data collection: an informed consent form, a demographic and clinical data form, a specimen collection form, and a laboratory test result form.

Laboratory equipment for blood specimen collection consisted of disposable syringes, 21G/23G needles, and Vacutainer tubes. Sputum collection used sterile containers with screw caps. Specimen processing used centrifuges, micropipettes, microcentrifuge tubes, and a -20°C/-80°C freezer. ELISA was performed using a microplate reader (450 nm filter), a microplate washer, a 37°C incubator, and a shaker. Three commercial ELISA kits were used to measure the biomarkers: sCD14, PGLYRP2, and FGA. Each kit contained coated microplates, recombinant standards, biotin-containing detection antibodies, streptavidin-HRP conjugate, TMB substrate, and stop solution.

The Human sCD14 ELISA Kit (Soluble CD14) was obtained from Elabscience Biotechnology Inc. (Houston, TX, USA), catalogue number E-EL-H0091. This kit has a sensitivity of 0.47 ng/mL, a detection range of 0.78–50 ng/mL, an intra-assay coefficient of variation (CV) of <5%, and an inter-assay CV of <8%. The Human PGLYRP2 ELISA Kit (Peptidoglycan Recognition Protein 2) was obtained from Fine Test (Wuhan Fine Biotech Co., Ltd., Wuhan, China), catalogue number EH1588. This kit has a sensitivity of 0.094 ng/mL, a detection range of 0.156–10 ng/mL, an intra-assay CV of <8%, and an inter-assay CV of <10%. The human FGA (Fibrinogen Alpha Chain) ELISA Kit was obtained from Cusabio Technology LLC

(Houston, TX, USA), catalogue number CSB-EL008642HU. This kit has a sensitivity of 0.39 ng/mL, a detection range of 1.56–100 ng/mL, an intra-assay CV of <8%, and an inter-assay CV of <10%.

Data analysis was conducted using two approaches, namely descriptive and inferential statistics. Categorical data are presented in the form of frequency (n) and percentage (%). Numerical data are presented using the mean ± standard deviation (SD). A homogeneity of variance test was conducted to meet the assumptions of the one-way ANOVA test. The analysis was conducted using SPSS Statistics version 25.0 with a significance value (α) of 0.05.

Ethical permission

This study was approved by the Poltekkes Kemenkes Manado in February 2025 (number DP.04.03/FXXX.28/451/2025).

RESULTS

Based on **Table I**, the number of respondents in this study was 180. Distribution by gender shows that male respondents are more dominant (53.9%) compared to female respondents (46.1%). In terms of age, the majority of respondents were in the 18–59 age group (51.2%), followed by the 60 years and above age group (39.4%), and the 10–18 years' age group (9.4%). Based on Body Mass Index (BMI), the largest proportion had an ideal BMI (38.3%), but obesity was also quite high (32.2%), while the underweight and overweight categories were 18.3% and 11.1%, respectively. Respondents' disease status was evenly distributed, namely healthy/normal (50.0%), TB with DM (25.0%), and MDR-TB (25.0%). The treatment status shows that some respondents are in the healthy group (50.0%), while the rest are undergoing treatment for varying durations, with the largest proportion at the 4th month of treatment (11.7%). The smallest proportion is in the 1st month and in the more than 6 months category (3.9% each).

Table I: Characteristics of Respondents

Variable	Number (n)	Percentage (%)
Gender		
Male	97	53.9
Female	83	46.1
Age		
10-18 Years	17	9.4
18-59 Years	92	51.2
60 years and above	71	39.4
Body Mass Index (BMI)		
Thin (≤ 18.49 kg/m²)	33	18.3
Ideal (18.5–24.9 kg/m²)	69	38.3
Overweight (> 25–27 kg/m²)	20	11.1
Obesity (> 27 kg/m²)	58	32.2
Disease Status		
Healthy/Normal	90	50.0
TB with DM	45	25.0
MDR-TB	45	25.0
Treatment Status		
Normal/Healthy	90	50.0
1 month	7	3.9
2 months	15	8.3
3 months	17	9.4
4 months	21	11.7
5 months	15	8.3
6 months	8	4.4
More than 6 months	7	3.9

Table II confirms that sCD14 levels in MDR-TB patients (102.89±29.45 ng/ml) were lower than in negative controls (108.52±14.23 ng/ml), while patients with TB-DM showed the lowest levels (77.42±42.31 ng/ml) with the highest variability. For PGLYRP2, MDR-TB patients had the highest levels (5.12±1.08 ng/ml) compared to controls (4.21±1.12 ng/ml) and patients with TB-DM (2.73±0.52 ng/ml), indicating its potential as a differentiating marker for MDR-TB. FGα levels were relatively similar between MDR-TB (34.21±7.89 ng/ml) and negative controls (34.89±5.43 ng/ml), with DM-TB being slightly lower (30.85±9.67 ng/ml).

Table II: Comparison of Serum Levels of Human sCD14, Human PGLYRP2, Human FGa in Healthy Individuals, TB Patients with DM and TBMDR Patients

Sample	sCD14 (ng/ml) Mean±SD	PGLYRP2 (ng/ml) Mean±SD	FGα (ng/ml) Mean±SD
MDR-TB	102.89±29.45	5.12±1.08	34.21±7.89
TB DM	77.42±42.31	2.73±0.52	30.85±9.67
Negative Control	108.52±14.23	4.21±1.12	34.89±5.43

Table III shows that the three variables between groups did not differ significantly ($p > 0.05$). sCD14 (Levene's statistic = 2.341; $p = 0.109$), PGLYRP2 (Levene's statistic = 1.856; $p = 0.169$), and FGA (Levene's statistic = 2.012; $p = 0.147$).

Table III: Test of Homogeneity of Variances

Variables	Levene's Statistics	Sig.
sCD14 examination	2,341	0.109
PGLYRP2 Examination	1,856	0.169
FGa Examination	2.012	0.147

Table IV shows that the sCD14 biomarker had a significant difference between groups ($p = 0.035$, $F = 3.112$), although it was not the best of the three biomarkers. The PGLYRP2 biomarker showed the most significant difference, with the highest F value ($p < 0.001$, $F = 14.496$). This is very different from the FGA biomarker, which did not show a significant difference between groups ($p = 0.377$, $F = 0.999$). This confirms that the FGA biomarker is less effective as a diagnostic predictor.

Table IV: One-Way ANOVA Test Results

Variables		Sum of Squares	Mean Square	F	Sig.
sCD14	Between Groups	5981,000	2990.500	3.112	.035
	Within Groups	39397.022	960,903		
	Total	45378.022			
PGLYRP2	Between Groups	29,016	14,508	14,496	.000
	Within Groups	41,033	1,001		
	Total	70,049			
FGa	Between Groups	116,998	58,499	0.999	.377
	Within Groups	2402.041	58,586		
	Total	2519.039			

Sandwich ELISA reaction on a well microplate ELISA parameters Human sCD14

ELISA Sandwich reaction on ELISA microplate wells, Human FGa parameters

ELISA Sandwich reaction on ELISA microplate wells, Human PGLYRP2 parameters

Figure 1: Sandwich ELISA reaction on a well microplate ELISA. All parameters (a. sCD14, b. FGa, c. PGLYRP2)

Figure 2: Optical Density measurement results on the ELISA Reader at a wavelength of 450 nm

DISCUSSION

Early and better detection is very important in cases of MDR-TB and TB-DM because both types of TB increase the burden of morbidity and disease complexity [16,17]. TB with DM comorbidity is often reported to worsen the condition of TB patients and increase drug resistance/multidrug resistance; this is why biomarkers for early and better detection are needed [18]. According to several studies, a history of DM and a history of TB can increase MDR-TB and are related to each other [19]. DM is often associated with several immune disorders resulting from delayed TB treatment in patients with diabetes mellitus. Theoretically, delayed treatment in TB patients can alter inflammatory/innate immunity biomarkers, which ultimately has the potential to affect the ability of external biomarkers to differentiate MDR-TB from other groups [20]. Diabetes mellitus (DM) can be a source of biological heterogeneity and influence serum biomarker levels. This is because DM can influence changes in the blood profile in TB patients with comorbid diabetes [21]. Previous research emphasized the importance of identifying candidate biomarkers, especially serum-based ones, to detect MDR-TB [22].

The research findings showed that the average sCD14 levels in the MDR-TB group (102.89±29.45 ng/ml) were lower than in the negative control group (108.52±14.23 ng/ml). In contrast, the DM-TB group showed the lowest average (77.42±42.31 ng/ml) and the greatest variability. CD14 plays an important role in the activation of the proinflammatory cascade because CD14 is a pattern recognition receptor on monocytes/macrophages. During inflammatory conditions, sCD14 can be actively released into the circulation through proteolytic breakdown. This makes sCD14 very promising for use as a TB biomarker because of its important role as a marker of innate immune system activation [23]. Often, sCD14 is also reported as a marker of inflammation, directly related to adipose tissue and insulin resistance, suggesting that sCD14 is part of the metabolic/diabetic spectrum [24]. The findings of this study indicate that TB-DM has a heterogeneous pattern that can increase inflammation and disrupt the adaptive immune response, which ultimately slows down TB healing [25]. The findings also showed that sCD14 levels in the MDR-TB group were not significantly higher than in the control group. This confirms that the discriminatory signal of sCD14 for drug resistance status appears to be descriptively weak [26].

The non-significant difference in sCD14 levels between MDR-TB and the control group suggests that drug resistance mechanisms primarily involving genetic mutations in bacterial drug targets do not fundamentally alter the host innate immune recognition pathway mediated by CD14 [27]. Since CD14 recognizes conserved pathogen-associated molecular patterns (such as lipoarabinomannan in Mycobacterium tuberculosis), and these structural components remain largely unchanged regardless of drug resistance status, the proteolytic release dynamics of sCD14 may not differ meaningfully between drug-sensitive and drug-resistant TB [28]. Furthermore, MDR-TB resistance mutations (e.g., in rpoB or katG) affect bacterial drug metabolism rather than the immunogenic surface structures that trigger monocyte/macrophage activation and subsequent shedding of sCD14. This mechanistic disconnect likely explains the descriptively weak discriminatory signal of sCD14 for drug resistance status [29].

The findings in Table 2 also show that PGLYRP2 has the highest value in MDR-TB (5.12±1.08 ng/ml), an intermediate value in negative controls (4.21±1.12 ng/ml), and the lowest value in DM-TB (2.73±0.52 ng/ml). DM significantly alters the immune response and biological profile across the spectrum of TB infection and has great potential in biomarker analysis [30]. DM is often associated with MDR-TB and can negatively impact its recovery. This suggests that

biomarkers that can differentiate between MDR-TB and DM-TB have the potential to be important for early identification of both [31].

Table II presents mean FGα values that are relatively comparable across the MDR-TB (34.21±7.89 ng/ml) and negative control (34.89±5.43 ng/ml) groups. In contrast, the DM-TB group exhibits a somewhat lower mean (30.85±9.67 ng/ml). The descriptive analysis suggests that the similarity in FGα values between the MDR-TB and negative control groups within this dataset infers that FGα does not provide a reliable indicator for differentiating MDR-TB from non-TB cases, given the specific population and sample size examined [32].

The broader biomarker literature demonstrates that individual markers frequently exhibit limited discriminatory power when assessed in isolation, yet gain diagnostic significance when contextualized within specific disease subgroups or combined with other analyses[33]. Indeed, inflammatory and acute-phase proteins, including fibrinogen-related molecules such as FGα are known to be modulated during tuberculosis infection as part of the host's systemic inflammatory response [34]. Notably, fibrinogen gamma (FG-γ) and fibrinogen beta (FG-β) have been identified among upregulated inflammation-related proteins in other inflammatory conditions [35], suggesting that fibrinogen chain variants respond meaningfully to immune perturbation.

There was a significant intergroup difference in sCD14 levels ($F=3.112$; $p=0.035$). This result implies that the three groups' mean sCD14 levels differed by at least one. Evidence that diabetes mellitus (DM) modifies immunity and inflammation in tuberculosis (TB) supports this interpretation, suggesting that immune biomarkers may more accurately reflect comorbid/metabolic status than drug resistance alone. Immunologically, the TB-DM interaction worsens treatment outcomes by impairing the clearance of Mycobacterium tuberculosis and increasing inflammation [30].

In **Table IV**, PGLYRP2 displayed the largest difference ($F=14.496$; $p<0.001$), which is in line with Table 2's trend of the greatest MDR-TB and lowest DM-TB. Since whole blood RNA-based signatures can be sensitive to cohort differences and sample processing, and their performance frequently deteriorates during independent validation, candidates deserving of additional research in TB transcriptomic biomarker screening are those that maintain consistent group separation across cohorts and pre-analytically [36]. In addition, systematic evaluations of therapy response biomarkers highlight the importance of replication to ensure clinical validity and demonstrate marker heterogeneity 37, in keeping with the strategy that prioritises prospective validation when developing monitoring indicators for drug-resistant tuberculosis [38].

Limitations and Future Research

This study has limitations that should be considered: Samples were collected exclusively from Manado, Indonesia, potentially limiting generalizability to other populations with different genetic backgrounds and TB strain prevalence. The biomarker analyses were performed individually; the synergistic potential of a combined biomarker panel has not been explored. The cross-sectional design precludes causal inference regarding biomarker-disease relationships. Future research should include: (1) a prospective, multi center validation study with a larger, demographically heterogeneous cohort; (2) a longitudinal design to track biomarker changes across treatment phases; (3) analysis of combinatorial biomarker panels to improve discriminatory performance compared to single markers; and (4) direct comparison with standard diagnostic modalities such as GeneXpert MTB/RIF and culture-based drug susceptibility testing. These steps will strengthen the evidence base and clarify the clinical role

of the studied biomarkers in TB management. The lack of longitudinal follow-up prevents the assessment of biomarker usefulness in monitoring treatment response or predicting outcomes.

CONCLUSION

Key findings from the study indicate that PGLYRP2 is the most promising biomarker in differentiating MDR-TB and provides the strongest statistical signal. Meanwhile, sCD14 is significant and shows differences affecting TB-DM. Meanwhile, FGα does not provide strong evidence of detecting MDR-TB and TB-DM. This aligns with previous studies that found a good biomarker is one that shows clear separation and remains strong even amid comorbidities such as DM. This is important because DM can worsen the immune response and increase resistance.

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AUTHOR CONTRIBUTION

Rambi EV: Conception, Design, Writing Draft, Revising, Agreement, Funding Acquisition, Finalization
Tumurang MN: Conception, Design, Writing Draft, Revising, Agreement, Funding Acquisition, Finalization
Sumenge D: Conception, Design, Writing Draft, Revising, Agreement, Funding Acquisition, Finalization
Tubmol MVL: Conception, Design, Writing Draft, Revising, Agreement, Funding Acquisition, Finalization

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