Review Article

Novel Potential Immune Response Biomarkers to Multidrug-Resistant Tuberculosis in the Last Five Years

Mutiara Shinta Noviar Unicha[1*], Wayan Tunas Artama[2], Niken Irfa Nastiti[1]
[1]Tropical Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]One Health Collaborating Centre/EcoHealth Resource Centre, Universitas Gadjah Mada, Yogyakarta, Indonesia

ABSTRACT

Rapid and accurate detection performs an important role in the control of raising MDR-TB. Currently, studies on biomarkers as targets for TB diagnostic tests using immune response products to indicate the presence, mycobacterial load, early markers, and activity, differentiation, and progression markers of TB infection are rapidly available. This systematic review aims to summarize the last five years of potential biomarkers studies from the immune response for MDR-TB rapid diagnostic development. The authors performed a literature search on four databases as ProQuest, EBSCO Academic Search, Universitas Gadjah Mada Online Library Journal Database, and Google Scholar, retrieved from January 2016 to December 2021. In total, 18,288 articles were identified and three tudies met the inclusion criteria. Several promising biomarkers were found for MDR-TB diagnosis purposes, such as sCD14, PGLYRP2, FGA, Indoleamine 2, 3- dioxygenase (IDO), and Complement Receptor 2 (CR2). A combination of sCD14, PGLYRP2, and FGA were bringing a diagnostic design with a higher sensitivity (94.7%) and specificity (80%) than the design of a single protein. Higher IDO activity towards the MDR-TB group than in the DS-TB group with a sensitivity of 87.50 %, specificity of 72.22 %. CR2 was the main focus due to its association with IL-6. After induction of CR2 peptide in a dose-dependent manner, the expression level of IL-6 was decreased significantly. It might because of CR2 peptide regulating the macrophages proinflammatory cytokines secretion to decrease the local inflammation of the immune response. These biomarkers are strong candidates for MDR-TB diagnosis due to their important role as the pathogenesis marker of MDR-TB. There is a need of further research to investigate those immune response products and their role to eliminate infection of Mycobacterium tuberculosis directly.

Keywords: Biomarkers, diagnosis, immune response, multidrug resistant, tuberculosis.

ABSTRAK

Deteksi cepat dan akurat berperan penting dalam pengendalian MDR-TB. Saat ini, studi tentang biomarker sebagai target untuk tes diagnostik TB menggunakan produk respon imun untuk menunjukkan keberadaan, bacterial load, penanda tahap awal infeksi, aktivitas, diferensiasi, dan penanda perkembangan infeksi TB tersedia dengan cepat. Tujuan dari tinjauan sistematis ini adalah merangkum studi biomarker yang berpotensi selama lima tahun terakhir dari respon imun untuk mengembangkan diagnostik cepat MDR-TB. Penulis melakukan pencarian literatur pada empat database seperti ProQuest, EBSCO Academic Search, Universitas Gadjah Mada Online Library Journal Database, dan Google Scholar dari Januari 2016 hingga Desember 2021. Total terdapat 18.288 artikel yang diidentifikasi dan terdapat 3 artikel yang meenuhi kriteria inklusi. Ditemukan beberapa biomarker potensial untuk diagnosis MDR-TB, seperti sCD14, PGLYRP2, FGA, Indoleamine 2,3- dioxygenase (IDO), dan Complement Receptor 2 (CR2). Kombinasi sCD14, PGLYRP2, dan FGA menghasilkan desain diagnostik dengan sensitivitas (94.7%) dan spesifisitas (80%) yang lebih tinggi dibandingkan desain protein tunggal. Aktivitas IDO lebih tinggi pada kelompok MDR-TB dibandingkan kelompok DS- TB dengan sensitivitas 87.50% dan spesifisitas 72.22%. CR2 menjadi fokus utama karena aktivitasnya terkait dengan IL- 6. Setelah induksi peptide CR2 dengan pemberian dosis terikat, tingkat ekspresi IL- 6 menurun secara signifikan. Hal ini mungkin karena peran peptide CR2 dalam mengatur sekresi sitokin proinflamasi

* Corresponding Author:
noviarshinta@mail.ugm.ac.id

makrofag untuk mengurangi peradangan lokal dari respon imun. Biomarker- biomarker tersebut merupakan kandidat kuat sebagai biomarker dalam mendiagnosa MDR-TB karena perannya yang penting sebagai penanda patogenesis MDR-TB. Diperlukan penelitian lebih lanjut untuk mengetahui produk respon imun tersebut dan peranannya dalam mengeliminasi infeksi Mycobacterium tuberculosis secara langsung.

Kata kunci: Biomarka, diagnosis, multidrug resistant, respon imun, tuberkulosis.

INTRODUCTION

Tuberculosis (TB) caused by the bacterial pathogen *Mycobacterium tuberculosis* is a chronic infection that affects the respiratory system, especially the lungs, and invades various tissues and organs, such as bones and central nervous system.[1–3] TB can be passed from an individual to others through droplets when coughing, sneezing, or conversing. Currently, there are 10.4 million new cases of TB over the globe with a total of 1.7 million deaths since 2013 through nowadays.[4,5]

Multidrug-resistant tuberculosis (MDR-TB) becomes a further problem of TB infection. These conditions include failure to respond to TB main therapy isoniazid and rifampicin, second-line therapy, short-term MDR-TB regimens, and long-term MDR-TB regimens.[3,6,7] The World Health Organization (2019) estimated that currently there are 484,000 MDR-TB cases in the world. The presence of *rpoB* gene mutation which arose due to insufficient administration of drug dose or incomplete therapy is strongly proven as the cause of MDR-TB.[8] Meanwhile, elimination of TB and MDR-TB depends on a wider scope of rapid diagnosis and treatments strategies. MDR-TB infection that has not been diagnosed early is harder to treat and has a high potential to infect a wide range of healthy individuals. This could lead to a high prevalence of MDR-TB, decrease the treatment stride, increased prevalence, new cases, and mortality from TB and MDR-TB. Therefore, rapid and accurate detection play an important role in the control of raising MDR-TB.[4,9,10]

However, clinical diagnosis for MDR-TB is progressing slowly. On the other hand, the efficiency of early detection is low.[11,12] Sputum-based diagnostic tests for active TB patients, such as patients with immunocompromise, diabetes, and child-aged, encounter problems of false-negative tests results.[13,14] In addition, sputum examination is less effective in patients with extrapulmonary tuberculosis. Invasive measures, such as taking samples from tissue or biological fluids, are needed to confirm the diagnosis. Interferon-gamma release assay (IGRA) test, for example Quantiferon-TB gold plus (QFT-Plus), is a rapid diagnostic test for active TB and latent TB that has a sensitivity of 94.1% and specificity of 97.3%.[8,14,15] But this test is infirm in diagnosing for drug-resistant TB/DR-TB. On the other hand, the Xpert MTB/RIF assay is a molecular based on RT-PCR test method which is time-saving to diagnose rifampicin resistant pulmonary TB.[11,16] This test has a sensitivity of 89% and a specificity of 99% for examination of sputum in pulmonary TB patients. Nonetheless, this test shows inconsistent accuracy results in extrapulmonary TB examinations.[12,14,16,17] Therefore, new diagnostic test innovations that could accurately predict active TB, latent TB infection (LTBI), and DR-TB are becoming priority needs nowadays.

Currently, studies on biomarkers as targets for TB diagnostic tests are rapidly available, notably the biomarkers from immune response products. The immune response to tuberculosis infection will produce secreted proteins such as cytokines as the marker of this disease progression in individuals.[18] Individual immune response products could play a role as biomarkers that indicate the presence, mycobacterial load, early markers, and activity, differentiation, and progression markers of TB infection. These

products are expressed with variation in the level, which could be used as benchmark and measurement to denote the progressivity of TB infection as active, latent, or drug resistant.[19–23]

Various studies focus on new discovered immune response products that have the potential to be used as biomarkers of MDR-TB. These biomarkers can be used as candidates for more efficient and accurate MDR-TB diagnostic targets.[14,24] This systematic review aims to summarize the last five years of potential biomarkers studies from immune response products for MDR-TB rapid diagnostic development.

METHODS

ProQuest, EBSCO Academic Search, Universitas Gadjah Mada Online Library Journal Database, and Google Scholar free web search engine were used to search relevant academic/ articles journals. Relevant articles were in English from the last five years January 1st, 2016 through 10th December, 2021. The searching process used "*Biomarkers or biological markers or biomarker or biological marker,*" "*drug resistance or antibiotic resistance*," and "*multidrug resistant tuberculosis or multidrug resistance tuberculosis or drug resistance tuberculosis*" as keywords. The inclusion and exclusion criteria were defined as below.

This study included the articles in English, original articles, experimental, and or observational studies, human or in vivo subjects, focused on immune response products, such as cytokines, and multidrug- resistant tuberculosis studies. This study excluded the studies that were conducted before 2016, only focused on tuberculosis without mentioned multidrug-resistant tuberculosis information, drug-susceptible tuberculosis, the study of therapy interventions, a geospatial or epidemiology studies, a clinical trials, retrospective, and systematic reviews.

Specific searched by subject thesaurus terms as "*Tuberculosis,*" "*tropical disease,*" "*Mycobacterium tuberculosis* drug effects," "*Mycobacterium tuberculosis,*" "*multidrug resistance,*" "*life science & biomedicine,*" "*infectious disease,*" "*immune response,*" "*drug resistance in microorganisms,*" "*drug resistance,*" "*diagnostic systems*," "*diagnosis,*" "*cytokines,*" "*biotechnology,*" "*biomarkers,*" "*biochemistry & molecular biology,*" "*antitubercular agents,*" "*antimicrobial resistance,*" "*antimicrobial agents,*" and "*antibiotic resistance*" were used. Titles and abstracts of all collected articles were screened with unblinded names of the articles' authors. The first author discussed with two co-authors when meeting any uncertainty during the screening process. The quality of articles was defined by indexed journal by Scopus minimum on quartile-2 (Q2).

RESULTS AND DISCUSSION

In total, 18,288 articles were identified. Of those, three studies met the inclusion criteria after a thorough screening process as included in this systematic review studies (Figure 1). The three selected studies are summarized in Table 1.

sCD14, PGLYRP2, and FGA

Soluble CD14 (sCD14) is reckoned as a good biomarker for activation marker of monocyte-macrophage. Increased level of sCd14 in plasma are often e related to poor prognosis of chronic infection.[25] Thus, this biomarker is used as strong predictor for morbidity and mortality.[26,27] Protein sCD14 plays a role in monocyte activation. In the early stage of TB infection, monocyte migrates to the infection locale and evolves as macrophages which may cause immune responses. Meanwhile, sCD14 level on the other infection, as example respiratory or lung disease, was increasing based on observation. Due to mass spectrometry strategy, sCD14 profusion in the MDR-TB group was lesser than in the DS-TB group, even it was upregulated in both. The possible reason of sCD14 decrease was decreasing of monocyte activation.[25,26,28]

Table 1. Summary of reviewed studies

	Title	Setting
Chen et al (2020)	Serum sCD14, PGLYRP2 and FGA as potential biomarkers for multi-drug tuberculosis based on data-independent acquisition and targeted proteomics	Groups of participants (healthy control, multidrug-resistant, drug-sensitive) Using liquid phase separation and mass spectrometry. Chromatography using a nanolitre flow HPLC system (Easy nLC-1200). Data-independent acquisition (DIA) technology is used for vast screening, qualitative, and quantitative analysis of a wide nest of samples. Parallel reaction monitoring (PRM) used to verify the identified diverse proteins
Shi et al (2019)	Plasma indoleamine 2,3-dioxygenase activity as a potential biomarker for early diagnosis of multidrug-resistant tuberculosis in tuberculosis patients	Groups of participants (healthy control, drug-sensitive, multidrug-resistant, lung cancer) Using high performance liquid chromatograpy-mass spectrometry (LC-MS/MS)
Yang et al (2019)	Significance of the differential peptidome in multidrug-resistant tuberculosis	Groups of participants (healthy control, multidrug-resistant, drug-sensitive) Differently expressed peptides were analyzed using liquid chromatography- mass spectrometry (LC-MS/MS) and their potential significance was analyzed using ingenuity pathway analysis (IPA)

Peptidoglycan recognition protein 2 (PGLYRP2) is known in mammals as direct antibacterial and considered as amidase by hydrolyzes bacterial cell wall.[28-30] PGLYRP2 roles in innate immune signaling are changing the recognition of peptidoglycan (PGN) via NOD1/NOD2 receptors.[28,30] The PGLYRP2 plays the important role for host defense toward bacterial lung infection by promoting macrophage activation synergized with TLR2 and TLR4.[30] It also regulates the neutrophils recruitment after respiratory infection. This study found that PGLYRP2 level was more markedly upregulated in the MDR-TB group than DS-TB group. This showed that its increasing related to individual's immune defense response.[28,31]
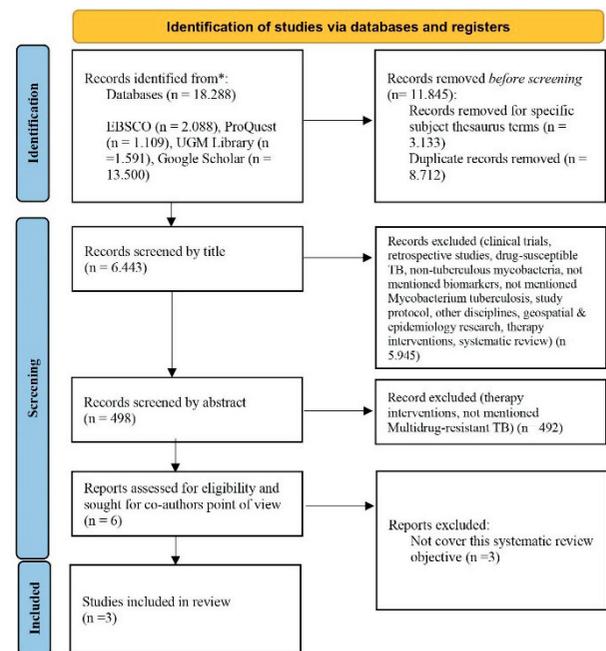
Figure 1. PRISMA diagram of the article selection procedure for related articles published between January 2016 and December 2021[29]

Fibrinogen alpha chain (FGA) is a variant of coagulation factor fibrinogen, as component of blood clot, which has molecular mass 420 kDa.[32] This study found that level of fibrinogen in MDR-TB group markedly increased rather than in healthy group. On the other hand, fibrinogen level in MDR-TB group was higher than DS-TB group. This may lead to indication of activated fibrinolytic system due to TB infection progression. Thus, FGA could be used to determine the severity of TB infection.[28,32]

Based on ROC curve analysis and multivariate logistic regression, sensitivity and specificity of sCD14 being biomarkers for MDR-TB and distinguished with healthy individual are 80% and 90%, respectively. Sensitivity and discussion should explore the significance of the results of the specificity of PGLYRP2 to detect MDR-TB

between healthy individual are 60% and 75%. Meanwhile FGA sensitivity and specificity are 75% and 95%. A combination of sCD14, PGLYRP2, and FGA were bringing a diagnostic design with a higher sensitivity (94,7%) and specificity (80%) than the design of a single protein.[28]

Indoleamine 2,3-dioxygenase (IDO)

Indoleamine 2,3-dioxygenase (IDO) is a derivate of tryptophan 2,3-dioxygenase (TDO), an intracellular, non-secreted enzyme that induces the tryptophan (Trp) to kynurenine (Kyn) degradation.[33,34] IDO activity is recognized to promote escalating mycobacteria burden and persistence in chronic infection due to its role to suppress CD4+T cell proliferation, promote the differentiation of CD4+CD25+Foxp3+ regulatory T cells (Treg) cells from naive CD4+ T cells, and instigate antigen-presenting cells (APC).[33–35] Higher IDO activity toward the MDR-TB group than in the DS-TB group and its correlation to lung cavity lesions in TB patients were observed. It makes MDR-TB patients present a decreased CD4+IFN-+T cell response and over-induced Treg activation. The cutoff for serum IDO activity in MDR-TB is 46.58 M/mM, with a sensitivity of 87.50%, specificity of 72.22%, and positive predictive value (PPV) of 73.68%. In this study, plasma Kyn and Trp – as two products of IDO metabolic pathway – were measured in MDR-TB patients and substantial differences between MDR-TB and DS-TB patients were observed continuously.[34,36] The IDO activity was also discovered to have a sturdy positive association with lung cavity pervasiveness and size. As a result, it can be concluded that MDR-TB and extensively drug-resistant tuberculosis (XDR-TB) are more likely to be associated with thicker walls and larger cavities. Hereinafter, the more extensive MTB demolition in the patients' lung parenchymal is associated with elevated plasma IDO activity, which might relate to immense cavity lung lesions (cavity prevalence and cavity size). This ensues a significantly higher risk of MDR-TB development and greater pathogen transmission. This study showed that IDO activity

plasma can be utilized as a potential biomarker for early MDR-TB identification.[34–36]

Complement Receptor 2 (CR2) Peptide

This study identified 40 expressed peptides from collected blood samples of enrolled patients. It found that there were four important differentially expressed peptides in multidrug-resistant tuberculosis: F2, CR2, COL5A2, and ITH4. Cell membrane protein CR2 or CD21 as peptide plays a role as promoting B lymphocyte responses and links the innate and adaptive immune response.[37,38]

Despite those four peptides, CR2 was the main focus due to its association with IL-6, one of the important proinflammatory factors that promote local inflammation.[38,39] After induction of CR2 peptide in a dose-dependent manner, the expression level of IL-6 was decreased significantly. It might be because of CR2 peptide regulating the macrophages proinflammatory cytokines secretion to decrease the local inflammation of the immune response. Through this mechanism, CR2 facilitates immune response to kill the *Mycobacteria tuberculosis*.[37–40]

SUMMARY

sCD14, PGLYRP2, and FGA may have potential as a diagnostic biomarker for MDR-TB when combined. It showed sensitivity and specificity as 94.7% and 80%, respectively. Otherwise, Indoleamine 2,3- dioxygenase (IDO) and Complement Receptor 2 (CR2) peptide are also strong candidates for MDR-TB biomarkers due to their important role as the pathogenesis marker of MDR-TB. There is a need for further research to investigate those immune response products and their role to eliminate infection of *Mycobacterium tuberculosis* directly.

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diving discussion to understand related theory through the first author.

CONFLICT OF INTEREST

The authors declare there is no competing interest.

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