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Neutrophil to lymphocyte ratio and immature granulocyte: assessing for promising parameters to monitor tuberculosis-diabetes mellitus patients

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ABSTRACT

Tuberculosis remains as a major global public health threat and infected more than >10 million cases worldwide. Nowadays, public have witnessed epidemiological shift between chronic and infectious disease globally. Diabetes mellitus as a non-communicable disease and on the other side, Tuberculosis as an infectious disease coexist in the same individual may became health challenge in the near future. DM's impact on clinical presentation and treatment outcome of TB remains poorly. Detecting and managing TB patients with DM comorbidity by routine laboratory screening provides an opportunity for monitoring patients' prognosis and decreasing disease severity to better outcomes. But in fact, not all laboratory services can provide complex yet expensive assays. Studies have shown Neutrophil to Lymphocyte Ratio (NLR) and Immature Granulocyte Percent (IG%) may be an option as an easy, quick, simple, low-cost, repeatable and reliable assays to monitor TB-DM patient's prognosis.

Keywords: tuberculosis, diabetes mellitus, neutrophil to lymphocyte ratio, immature granulocytes, laboratory

INTRODUCTION

Tuberculosis (TB) persists as a major global public health threat and the leading causes of death worldwide. Based on projections, approximately TB has infected about a quarter of global population. More than >10 million cases in 2022 and >1.6 million death were reported globally. 30 High TB Burden Countries contribute to 80% TB cases and it remains a challenge for health authorities to achieve "End TB" strategies in 2030 [1].

Recently, members of the public have witnessed the development and progression of new public health burdens, which include two different diseases: Tuberculosis (TB) as an infectious disease, and on the other hand Diabetes mellitus (DM), as a non-communicable disease. This new syndemic progression is sky rocketing and represents a health challenge in the near future [2]. The epidemiological shift occurring when both chronic and infectious illnesses coexist not only in the same population but also in the same individual is exemplified by the comorbidity of TB and diabetes [3].

International Diabetes Federation (IDF) reported >500 million people are currently living with diabetes and it is estimated this number will increase gradually to 783 million diabetics globally in 2045 [4] due to lack of physical activity, lack of fiber and poor diets. While diabetes mellitus (DM) is primarily urban, it is also becoming more prevalent in semi-urban and rural areas, often undiagnosed and complicated by another complication [5]. DM causes alterations in the immune system, increasing susceptibility risk to mycobacterium tuberculosis

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infection, as well as drug resistance risk, treatment failure, morbidity and recurrent disease [6,7]. A prospective cohort study reported 18% of TB patients had diabetes and these individuals had worse outcomes than non-diabetic pulmonary TB patients [8].

World Health Organization (WHO) conjointly with the International Union against Tuberculosis and Lung Disease (IUALTD) have recommended the "bi-directional" screening and integrated management for TB-DM disease in high burden countries. But in low and middle-income countries, the health system and management frequently are undependable and not adequate to respond to those dual burden diseases [7]. The incidence and worsening prognosis of TB-DM patients may become higher year by year if controlling and monitoring efforts are not implemented. Detecting and managing TB patients with DM comorbidity by routine laboratory screening provides an opportunity for monitoring patients' prognosis, decreasing disease severity for better outcomes [5]. Maintaining optimal disease outcomes and minimizing toxicity, drug interactions, and other issues when managing TB-DM optimally is crucial yet challenging.

Mostly, scientific literature focuses on the TB-DM prevalence, with barely any kind of evidence to help clinicians manage TB-DM patients clinically. Management and strategies to prevent diabetic patients infected with TB and vice versa is important, but we cannot neglect following-up patients that were already diagnosed by TB-DM. Routine laboratory assays can be the choice for monitoring TB-DM patient's prognosis and infection level yet providing data for clinicians to obtain the best treatment. But it remains a challenge to choose the most quickly, low-costly, and easily obtained result. White blood cell count (WBC) is a well-known assay to evaluate inflammation. Inflammatory response is valuable to the TB pathophysiology [9].

Immature Granulocytes percentage (IG%) recently being studied and able to be a marker for sepsis diagnosis and more indicative than other clinical parameters such as C-reactive protein, and IL-6 [10]. TB patients have lower lymphocytes counts, higher neutrophil and higher monocyte counts also stimulating increasing immature neutrophils numbers as defined by "left shift" or increasing immature neutrophils divided by total granulocyte [11,12]. Neutrophil to Lymphocyte Ratio (NLR) is emerging as a new marker of inflammation in many diseases including lung diseases [12,13]. Both NLR and IG% are automatically provided by hematology analyzer through routine blood count. It does not need an additional workload and cost, yet is easily repeatable [12]. This article discusses NLR and IG% as an easy, low cost and promising routine laboratory assay to follow up TB-DM patients' inflammation prognosis.

TB-DM PATHOPHISIOLOGY AND OUTCOME

Diabetes Mellitus is a serious, chronic disorder with major adverse effects on peoples' lives, families, and societies and remains among the top 10 causes of death in adults [4]. DM characterized as hyperglycaemia caused by insufficient insulin production, insulin resistance, or both [7]. T2DM (Type 2 Diabetes Mellitus) contributes to at least 90% of the whole DM cases worldwide. All DM types are progressive diseases that lead into many complication after effects.

DM patients show compromised and alteratered innate immunity leading to the dysfunction of neutrophils, macrophages, natural killer (NK) and any other cell components [14]. Immunity disorders can be affected by high-level glucose levels leading to Advanced Glycation End Products (AGE). Inflammation is vital for host response in order to fight against pathogens that infected the body. As a response for *M. tuberculosis* infection, cytokine secreted by innate immune cells and adaptive immune cells collaborate to eliminate microorganisms [15]. Diabetic macrophages have increased CCR2 expression and reduced CD14 receptor expression, which contributed to restrain monocytes migration to the lungs and also reduced MTB phagocytosis. Cytokines such as IL-1β, IL-6 and TNF-α production are lower in diabetes patients compared to healthy subjects. It also reported an association between glycaemic control and cytokine production [16].

TB-DM patients are more infectious when diagnosed, as they appeared to have a higher bacterial load also more likely to have pulmonary cavities and haemoptysis [14]. Uncontrolled glycemic levels increas infection risks including *M. tuberculosis* infection, worsening prognosis, and also increasing the risk of multi-drug resistance to TB. DM increased the risk of death in individuals with active tuberculosis and relapse risks after treatment completion. Another study stated that patients with TB-DM were reported to have other comorbidities. A person with DM is 1.8 to 9.5 times likelier to be infected with TB compared to non DM individuals [14].

TB-DM PATIENTS MONITORING MANAGEMENT AND CHALLENGE

World Health Organization suggests performing any collaborative care to TB-DM patients with collaborative health services focused in to three aspects: (1) Establish a strong collaborative services mechanism; (2) detecting and monitoring TB in DM patients; (3) detecting and monitoring DM in TB patients (bi-directional care). Routinely screening laboratory assays for DM in TB patients and, vice versa, routinely screening TB for DM patient (bi-directional screening) are likely to give another chance for early diagnosis, better prognosis follow-up and treatment management plan in the future.

Glycemic control in DM patient is performed to maintain glycated haemoglobin (HbA1c) <7% throughout the treatment. But in fact, this target seems hard to obtain because in the early phase of TB infection, active TB will initiate hyperglycaemia. On the other hand, Rifampicin also interacts with DM drugs leading to decreasing drug performance [6]. Glycemic control and strategies for minimizing the risk of cardiovascular diseases are part of diabetes care during anti-tuberculosis treatment which aims to improve TB treatment outcomes and reduce DM-related morbidity and mortality [17]. Maintaining glycemic level control itself cannot represent patients' whole state of health. It needeeds other laboratory findings to assess disease severity. Hematology assay itself is likely the most preferable assay in the medical field due to being simple, easy, quick and repeatable. While discussing about infectuous diseases, white blood cells count is dependable to represent the patient's state.

NEUTROPHIL TO LYMPHOCYTE RATIO AS A PROGNOSTIC BIOMARKER

Neutrophils are the first cells which respond to bacterial infections and also dominate the acute inflammation phase. These cells also have a leading function in innate immunity before adaptive immunity is formed. Neutrophils are well-known broadly as pivotal cells in the defense against bacterial infection and can eliminate bacteria effectively because of their huge stocks of proteolytic enzymes and quick synthesis of Reactive Oxygen Species (ROS). This cell also releases a web-like structure called neutrophil extracellular traps (NETs) to immobilize and eliminate microorganism like bacteria [18]. Proinflammatory cytokines and chemokine modulator immunity are secreted by neutrophils to initiate other cells recruited into the infection site. Activated neutrophils contain many enzymes and antimicrobian molecules that kill microbes [19].

Abnormal number of blood neutrophils counted from full blood count is a cheap, fast and ubiquitous laboratory method for inflammation assessment. Neutrophil to Lymphocyte ratio (NLR) has attracted attention as a new inflammatory marker [18]. It is calculated easily from total neutrophil count derived by total lymphocyte count. NLR can represent both innate and adaptive immunity system by neutrophil and lymphocyte [19]. High level NLR can indicate the course of chronic inflammation. Therefore, NLR is more stable and less influenced by pathological and physical factors than another leukocyte assays.

Several studies reported useful NLR results on the prognosis markers of several diseases such as lung diseases [20,21], diabetes and cardiovascular disease [22,23], cancer [24,25] and sepsis [26]. NLR in early stage would help identify adverse outcomes and observation plans in Community Acquired Pneumonia [13]. High NLR ≥5 were associated with pulmonary cavitation yet increased severity of inflammation also increased the risk of mortality and exacerbation in chronic obstructive pulmonary disease (COPD) (OR: 2.9) [27]. Another study stated that NLR can support in differentiation of tuberculosis and sarcoidosis [12]. Cut-off value of NLR for one-year mortality in miliary tuberculosis is 5.2 and NLR ≥5 remarkable decreased in survival rate [28].

NLR has also been used in DM care and management control by many studies. Meta-analysis conducted by Adane and colleagues confirms that NLR value was significantly associated with poor glycemic control in T2DM patients (OR=1.50 – 95%CI: 1.30-1.93) [29]. NLR can be used as a predictive prognosis in diabetic foot ulcer patients to undergo amputation and other implications. Calculating NLR is easy and elevating the number of NLR can predict worsening inflammation in diabetic nephropathy patients. Cardiovascular disease (CVD) risk is increased in DM patient and increased NLR can be used to predict CVD in T2DM patients [30].

Both TB and DM conditions regularly require monitoring to achieve a better outcome. Offering NLR as a regular assay procedure is very promising. Elevated NLR physiologically shows the inability of the immune system to suppress infection [25]. NLR suggest a low-cost, non-invasive, quick and early opportunity to asses TB-DM patient prognosis and status, and allow physicians to make better decisions about treatment and therapy.

IMMATURE GRANULOCYTE AS A PROGNOSTIC INFECTION BIOMARKER

During infection, mature neutrophils are proliferating to kill bacteria. Then, immature neutrophils will enter the bloodstream. This "left-shift" infection response is defined as an increased ratio of immature granulocytes to total granulocytes [10]. Immature granulocytes themselves consist of mainly promyelocytes, myelocytes and metamyelocytes, but do not include band form neutrophils [31]. Immature granulocyte percentage nowadays is automatically assayed and calculated by hematology analyzer. It does not require any other reagents, additional workload, low cost yet repeatable by routine blood count.

Normal IG% in healthy population may be varying (0.0-0.1%). Diabetes patients tend to develop any other disease besides TB, such as cardiovascular complication, renal disease, etc. [32]. In cardiovascular disease, IG% were assessed as a prognostic value and predict risk of mortality [33]. In lung disease management, IG% can be useful as a predictive marker of COVID-19 [34] and distinguish severe

TABLE 1. Studies investigating IG% as predictor and prognosis biomarkers

Study	Design	Case	N	Result
Ha et al [31]	Retrospective	Sepsis	184	IG% could discriminate between complicated and uncomplicated sepsis with cut off value 0.5%
Korkut et al [33]	Retrospective	STEMI	146	IG% was shown to predict mortality in STEMI patient at a cut-off value 0.65 with sensitivity 72.2% and specificity 77.8%
Selvi et al [34]	Retrospective cohort	COVID-19	252	IG% >0.03 with 66.7% sensitivity and 72.3% specificity was significant in the predictivity of COVID-19
Alisik et al [35]	Retrospective	COVID-19	2247	IG% may be useful to distinguish severe COVID-19 patients at the time of admission with cut off value >0.03
Ayres et al [37]	Cross-sectional	Sepsis	301	IG% <2.0 are helpful on the exclusion of sepsis diagnosis with specificity 90.9% and sensitivity 38.5%
Huang et al [38]	Prospective cohort	ARDS (acute respiratory distress syndrome)	1933	Area Under Curve IG% for predicting ADRS is 0.821 (95% CI 0.794-0.849) and cut-off value 0.65% with sensitivity 90.85 and specificity 60.4%

COVID-19 patients [35]. Elevated IG% found to be correlated with elevated C - reactive protein and procalcitonin than healthy or control group. It is associated with an acute-phase response in which activated bone marrow to release IG into bloodstream [36]. Several studies conducted with IG% as a marker shows in the table below (Table 1).

Increased IG% in the peripheral blood is directly related to systemic inflammation intensity. This cell can be created when bone marrow is stimulated during bacterial infection, trauma and sepsis. Early response of IGs is promising to be an indicator of decreasing immune response and inflammation severity. It may be more accurate than total white blood count [38]. Elevated IG% may be an indicator for tuberculosis severity infection.

NLR AND IG AS A PROMISING TB-DM PROGNOSIS

The high interest regarding biomarkers and biosignatures for active TB detection and monitoring is encouraging. But in fact, only a small proportion of those markers are suitable in many kinds of laboratory and health service providers. TB-DM as a progressive yet infectious disease require regular follow-up and treatment strategies to reduce worsening prognosis and mortality throughout the treatment. Immunological and biomolecular assays are dependable but require complex and expensive technology. Biomolecular assays are promising to predict adverse outcomes of pulmonary TB. Thus, limited health services with limited human resources and limited laboratory settings cannot accommodate these complex assays to be done.

Hematological parameters have a crucial role in treatment strategies and monitoring treatment of TB-DM cases. It can influence patients' outcome afterwards. Hematological findings (NLR and IG%) are cost-effective and able to provide clinically useful information to support the management and care of TB-DM patients through treatment to improve outcomes, survival rates, and quality of life [39]. CRP (C - reactive protein) is a well-known assay and used widely in many laboratory services. However, it lacks specificity as an inflammatory biomarker [36]. Nowadays, health services seek a promising assays to provide quick and useful information in order to plan the next treatment and care management. NLR and IG% counts are proved by many studies to be promising and reliable parameters as prognostic biomarkers in many diseases. Therefore, it needs further studies to determine cut-off value including AUC, ROC, specificity and sensitivity in TB-DM cases.

CONCLUSION

To manage TB-DM patients, health facilities used to give more attention and care management in order to decrease severity, mortality risk, and treatment failure. Patients should be monitored regularly to maintain their condition. NLR and IG% can be promising assays for TB-DM prognosis assay. Both NLR and IG% counts provide quick, reliable, low cost and simple results.

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