J Clin Tuberc Other Mycobact Dis 11 (2018) 10–16

Contents lists available at ScienceDirect

J Clin Tuberc Other Mycobact Dis

journal homepage: www.elsevier.com/locate/jctube

Use of classification and regression tree (CART), to identify hemoglobin A1C (HbA_{1C}) cut-off thresholds predictive of poor tuberculosis treatment outcomes and associated risk factors

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ARTICLE INFO

Keywords:
Fractal geometry
Hollow fiber
Tuberculosis outcomes
Hyperglycemia

ABSTRACT

Background: Rifampin-based therapy potentially exacerbates glycemic control among TB patients who are already at high risk of hyperglycemia. This impacts negatively to the optimal care of TB- diabetes mellitus co-affected patients. Classification and regression tree (CART), a machine-learning algorithm impervious to statistical assumptions is one of the ideal tools for clinical decision-making that can be used to identify hemoglobin A1C (HbA_{1C}) cut-off thresholds predictive of poor TB treatment outcomes in such populations.

Methods: 340TB smear positive patients attending two peri-urban clinics were recruited and prospectively followed up for six months. Baseline HbA_{1C} and random blood glucose (RBG) levels were determined. CART was then used to identify cut-off thresholds and rank outcome predictors at end of therapy by determining Risk ratios (RR) and 95% confidence interval (CI) of each predictor threshold. Fractal geometry law explained effect of weight, while U-shaped curve explained effect of HbA_{1C} on these clinical outcomes.

Results: Of the 340 patients enrolled: 84%were cured, 7% completed therapy and 9% had unfavorable outcomes out of which 4% (n = 32) had microbiologic failure. Using CART HbA_{1C} identified thresholds were >2.95%, 2.95–4.55% and >4.55%, containing 8/11 (73%), 111/114 (97%) and 189/215 (88%) of patients who experienced favorable outcomes. RR for favorable outcome in patients with weight <53.25 Kg compared to >53.25 Kg was 0.61 (95% CI, 0.45–0.88) among patients with HbA1C >4.55%. Simulation of the CART model with 13 patients data failed therapy revealed that 8/11 (73%) of patients with HbA1C <2.95%, 111/114 (97%) with HbA_{1C} between 2.95% and 4.55% and 189/215 (88%) of patients with HbA1c >4.55% experienced microbiologic failure.

Conclusion: Using fractal geometry relationships to drug pharmacokinetics, low weight has profound influence on failure of anti-tuberculosis treatment among patients at risk for diabetes mellitus.

Introduction

Tuberculosis (TB), like other infections, can worsen glycemic control and complicate the clinical management of Diabetes mellitus (DM) [1–3]. The dual burden of TB and DM (gestational, type I and type II) have increased over the past decade with DM prevalence increasing in countries already afflicted with a high burden of TB [3]. The coexistence of two conditions presents a serious threat to global public health and patient clinical care resulting into worse clinical outcomes across the entire spectrum of either disease [2,4]. In one study, 7.5% (95% CI: 4.1%−11.5%) of TB incidence cases were attributable to hyperglycemia [5]. A south African cohort further demonstrated a correlation between active TB and the level of glycosylated hemoglobin (HbA1c) with a hazard ratio of 1.39 (95% CI: 1.18–.63) per unit increase [6,7]. In addition to the well-established contribution of DM to increased TB susceptibility, findings from most observational studies indicate that this co-morbidity is associated with delays in TB clearance during treatment, treatment failures, death, relapse, disease severity and re-infection [2,5]. Diabetic TB patients' management can play a critical role in understanding TB transmission dynamics [8]. The link between DM and TB and the implementation of the collaborative framework for care and control have thus widely been recommended as a means to potentially stimulate and strengthen the scale-up of non-communicable disease care and prevention programs, which may help in reducing not only the global burden of DM but also the global burden of TB [8–10].

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https://doi.org/10.1016/j.jctube.2018.01.002
Received 28 September 2017; Received in revised form 18 January 2018; Accepted 23 January 2018

In Kenya, the TB program recommends bidirectional screening, though there is dearth of data on performance of specific TB tests in individuals with DM, specific DM tests among TB patients, and screening and preventive therapy for latent TB infections in individuals with DM. Some of these can be attributed to the poor data management system in our health facilities. Studies indicate that TB patients with DM have a lower concentration of TB drugs and a higher risk of drug toxicity than those without diabetes [11]. In addition good glycaemic control, which reduces long-term DM complications and could also improve TB treatment outcomes, is hampered by chronic inflammation, drug-drug interactions, suboptimum adherence to drug treatments, and other factors [9,11,12]. Besides drug treatments for TB and DM, other interventions, such as education, intensive monitoring, and lifestyle interventions, might also be needed, especially for patients with newly diagnosed DM or those who need insulin. From a health systems point of view, delivery of optimum care and integration of services for tuberculosis and diabetes is a huge challenge in many countries more specifically resource limited setting.

DM screening among TB patients is now widely recommended, especially in setups with high DM prevalence [12]. A case example is India and the Pacific Islands region's TB control programs [13,14]. Despite these efforts, the best time and methods to diagnose for DM diagnosis among TB patients remains unclear [15–17]. In one of the observational studies, it was found that glycemic status was influenced by radiological manifestations of diabetic pulmonary TB [15,16]. DM pevalence rises steeply with age, but the most efficient age cut-off for screening is also unclear and varies among populations [18]. Blood glucose concentrations measurement at a single point in time might lead to a false diagnosis of DM in patients with TB because they could have intermittent hyperglycaemia through induction of insulin resistance, mediated by inflammation. TB [19,20]. Repeat testing could identify transient Hyperglycaemia concentration assessment is thus the only diabetes test that shows average glycaemia over time and in a single study [21,22], as it is more sensitive than fasting blood glucose when used as a screening test for newly diagnosed diabetes in patients with tuberculosis [22].

Though HbA_{1c} concentration assessment has been indicated as the most preferable test method for DM among TB infected patients, hyperglycemia levels predictive of poor clinical outcomes among patients with both DM and TB, for which clinicians must target for optimal care, is not well defined [18–20]. It has been shown that experimental hollow-fiber models of tuberculosis chemotherapy, and in TB patients, that pharmacokinetic variability directly leads to failure of TB therapy [23,24]. Moreover, rifampin is known to exacerbate hyperglycemia in patients starting TB therapy, suggesting that therapy in patients at risk of TB can be optimized and personalized [23]. To better inform TB programs, we sought to examine and rank factors predictive of clinical outcomes in routine low-resourced clinical settings using CART analysis. We also determined thresholds for those predictors that could be used for clinical decision-making. The focus of this study was TB patients at risk for DM. Previously; the hypothesis has been used to explain poor long-term outcomes in supposedly 'adequately' treated tuberculosis patients: wherein systemic tuberculosis infection produces early organ damage that leads to death in the long-term [25,26]. In this study we proposes the use of boosted classification and regression trees (CART) to determine baseline HbA_{1c} and random blood glucose (RBG) levels predictive of clinical outcomes in tuberculosis patients with/out diabetes mellitus. CART is an agnostic machine-learning algorithm more adept for data-driven pattern recognition, selecting predictors and their thresholds based on reproducible models.

Methods

Definition of terms

Clinical outcomes were defined using WHO and Kenyan tuberculosis program guidelines standard operational terms (http://nltp.co.ke/guidelines/) 27,28. The primary analyses compared favorable versus unfavorable outcomes at end of treatment. The secondary analyses only compared "cures" versus "failures" at similar time points as is the standard practice when examining chemotherapy efficacy.

Study design

We carried out a prospective cohort in two peri-/urban counties of Kenya (Kiambu and Nairobi) between February 2014 and August 2015. We enrolled patients aged >15 years who were TB smear positive and were not pregnant (Pregnant women are high risk group of Gestatinal DM) at time of diagnosis. TB culture test was used to confirm all the positives. Ethical approval was obtained from the Kenyatta National Hospital Ethical Research Committee. We collected one venous blood draw at baseline in two separate tubes (one for fasting or random blood glucose levels and the other for HbA1c levels). Each patient then had physical examination and questionnaire administered by trained healthcare personnel where detailed history, including signs and symptoms of diabetes mellitus, cigarette smoking and other life-style information were ascertained. Patients were followed prospectively at two, three, five, six months and at end of therapy. During each visits we assessed adherence treatment and treatment outcome with sputum microscopy examination. The initial sputum examinations were submitted for culture and pathogen identification. Patients were examined at each visit for both TB and DM.

Care and treatment

New tuberculosis patients were put on a six-months category I regimen comprising of 2 months of isoniazid, rifampin, pyrazinamide and ethambutol followed by four months of isoniazid and rifampin.. Previously treated patients, including those who had failed prior therapy were put on category II regimen which is similar to category I only that, streptomycin is additionally administered for the first two months, while the other four drugs is prolonged by one month and isoniazid, rifampin and ethambutol are given for a further five more months. Dosing was as per Daily fixed dose combinations formulations as per NTLD and WHO guidelines were given using directly observed Treatment, short course (DOTs) [28].

Glycosylated hemoglobin (HbA1c) measurements and laboratory quality assurance

HbA1c measurement was performed on Ethylenediamine-tetraacetic acid (EDTA) whole blood samples within 4–6 h of sample collection using cation exchange high performance liquid chromatography (HPLC). The assay values were standardized to the Diabetes Control and Complications Trial - Deflection Check: 0.5, Discreteness Check: 0.1 Abs, Sensitivity Check: 0.14, Blank Level Checks −0.1- −0.7. Laboratory procedures were performed as per manufacturer instructions. Commercial controls consisting of HbA1c Abnormal Low, Normal and Abnormal High and HbA1c calibrators were included during the assay procedure. HbA_{1C} and random blood glucose results were then issued to patients to receive appropriate further management after consulting with their physician.

Data analyses

Richardson-Mandelbrot log-log plots were used to examine fractal behavior [29,30]. We modified the equation to $f(t) \sim \left(\frac{t}{tp}\right)^{-q}$ to circumvent obvious concavity and inflection point estimate from the cumulative distribution plot. Observed variable value is denoted by t while tp denotes observed value at the inflection point. Since we were interested in physiological function in addition to morphological