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Neural network models for supporting drug and multidrug resistant tuberculosis screening diagnosis

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ABSTRACT

Tuberculosis (TB) is the leading cause of global mortality among communicable diseases. The diagnosis of Drug-Resistant Tuberculosis (DR-TB) demands even more attention, leading to longer treatments and higher deceased rates. All diagnostic methods available have deficiencies in their detection rates, time release results, or have a higher cost and need a complex infrastructure to setup. New molecular diagnostics, such as the Xpert MTB/RIF assay, have great potential for revolutionizing the diagnosis of Rifampicin Resistance (RR). But, a positive RR result with this test should be carefully interpreted and take into consideration the risk of Multidrug-Resistant TB (MDR-TB) according to its prevalence, locally. Therefore, the development of screening approaches for DR/MDR-TB suspects would help to identify those should be tested by Xpert MTB/RIF. This work develops Artificial Neural Network (ANN) models considering data from presumed DR/MDR-TB subjects according to the National Guidelines at Rio de Janeiro/Brazil, attended in reference centers in Rio de Janeiro, from Feb 2011 and May 2013. Subjects aged 18 years or older, and results were compared with models based on Classification And Regression Trees (CART). Practical operation at different epidemiological scenarios are considered by constructing models using different variable selection criteria, so that environments with low resource conditions can be assisted. Among 280 presumed DR-TB cases included, 38 were DR-TB, 48-MDR, 32-Drug-Sensitive and 162 with no TB. Between DR-TB and non DR-TB, the sensitivity and specificity reached 95.1%(±5.0) and 85.0%(±4.9), respectively. The promising results of clinical score for DR/MDR-TB diagnosis indicate that this approach may be used in the evaluation of presumed DR/MDR-TB.

1. Introduction

Tuberculosis (TB) is the leading cause of global mortality among communicable diseases. Nearly one-third of the world's population is infected with the Mycobacterium tuberculosis. An estimated 9.6 million new cases of TB develop annually and 1.8 million persons die from the disease [1]. The emergence of Drug-Resistant (DR: resistant to at least one drug), Multi-Drug Resistant (MDR: resistant to rifampin and isoniazid) and Extensively Drug-Resistant (XDR: MDR + resistant to fluoroquinolones and aminoglycosides) TB has exacerbated the threat to public health and created a renewed sense of urgency to TB control. Globally, 3.5% of new TB cases and 20.5% of previously treated cases are estimated to have MDR-TB, and 55% of reported TB patients estimated to have MDR-TB were not detected in 2013, leading to continued spread of drug-resistant organisms in the community [2].

Since 2006, following the STOP TB Global Plan, new diagnostic approaches were proposed by WHO, e.g. the use of clinical-radiological algorithms that include liquid culture or molecular testing methods, such as Xpert MTB/RIF, in regions with a high prevalence [3]. The Xpert MTB/RIF assay has great potential for revolutionizing the diagnosis of DR-TB (rifampicin/RR). But, a positive RR result with this test should be interpreted by a specialist. The risk of MDR-TB must also be taken into consideration, as higher false positive results with Xpert MTB/RIF are expected in health units with prevalence of MDR-TB lower than 10% (usually presumed DR-TB subjects attended at the primary and second health care sector, in lower and middle income countries) [4].

In Brazil, several advances in TB control in the past 10 years have been obtained, but serious obstacles need still to be overcome, including the low rate of detection of DR-TB and the high morbidity and mortality among MDR-TB cases. In 2012, culture was performed on 17.4% of TB reported cases, and only in 28.1% of

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previously treated TB cases [5]. In 2013, 503 MDR-TB cases were reported, 220 (43%) were diagnosed in Rio de Janeiro state. Among those that received second line regimen, favorable outcome were observed only in 62%. Our group observed a significant reduction, using the time from sample collection to start appropriate treatment for patients with DR-TB as primary outcome for Xpert (mean 15 days) compared to MGIT (mean 40.5 days) arm. Nevertheless, a high rate of treatment by clinical diagnosis before test results remained in both arms [6].

Due to these operational issues, the high cost of Xpert MTB/RIF and its low positive predictive value ($\leq$ 80%) in regions where TB prevalence is lower than 10% among all TB suspects, screening tests have been proposed and discussed in order to assist the identification of individuals with a higher probability of having the disease [7]. WHO made recommendations on screening for TB in adults and children aged 10 years or older, but not for DR/MDR-TB [8].

The "Global End Tuberculosis (TB) Strategy" aims to reduce TB deaths and incidence in all countries to levels currently observed in high-income countries. This strategy is based on three pillars: integrated, patient-centered care and prevention (Pillar 1); bold policies and supportive systems (Pillar 2); and intensified research and innovation (Pillar 3) [9]. Therefore, innovative approaches are warranted, as improving early DR-TB diagnosis and reducing mortality [10]. The development of screening approaches for presumed DR/MDR-TB subjects would help to identify those cases that should be tested by XpertMTB/RIF.

We propose the development of a clinical score to support screening presumed DR-TB patients sent to the reference centers in Rio de Janeiro, Brazil. DR/MDR-TB and Drug-Sensitive Tuberculosis (DS-TB) diagnoses are evaluated solely by considering symptoms and historical factors. The study focused practical operation at different scenarios by constructing models using different variable selection criteria, so that environments with low resource conditions can be assisted. Artificial Neural Network (ANN) models are developed, exploiting their capability to extract non-linear correlations and approximate any continuous function [11], and their results are compared to models based on Classification And Regression Trees (CART) [12].

This paper is organized as it follows. Section 2 reviews the related work. Section 3 describes the method applied in this work, including dataset description, the computational models, and the way relevance of variables is estimated. Section 4 shows the achieved results and the corresponding discussion from a clinical perspective. The conclusion is derived in Section 5.

2. Related work

Several studies have been made in order to assist patient screening through the development of a clinical score by computational methods. Examples of such applications can be found in the literature, such as the support in the diagnosis of cardiac ischemia [13] and acute coronary syndrome [14] in patients presenting to the emergency department with chest pain, diagnosis of acute upper gastrointestinal hemorrhage [15], prediction of mortality in head trauma [16], pulmonary insufficiency and tricuspid insufficiency [17], gastric carcinoma [18], and trauma outcome prediction [19]. Clinical scores appear as a fast, low cost, and easy-to-use solution that can help to support screening decisions, avoiding more invasive exams, and expediting patients routing, crucial when handling infectious diseases.

When considering the prediction of TB diagnosis, studies have developed score systems by using different computational methods in distinct scenarios. Based on logistic regression, Solari et al. constructed a scoring system to predict pulmonary TB of patients with respiratory symptoms. Information consisted of clinical symptoms, past medical history, demographic data and exams results, and the score attained 93% sensitivity and 42% specificity [20]. Logistic regression and CART models were presented by Mello et al. to assess the diagnose of smear negative pulmonary tuberculosis for outpatients in areas with scarce resources. Models were constructed by using patients' symptoms, physical signs and chest X-rays. The predictive models showed sensitivity ranging from 64% to 71% and specificity ranging from 58% to 76% [21]. Also using CART, Aguiar et al. presented a model for predicting pulmonary TB in hospitalized patients, admitted with clinical suspicion of TB, in a high prevalence area. Clinical data, potential predictive factors for TB diagnosis, and radiologic test results were considered, reaching sensitivity and specificity of 60% and 76%, respectively [22].

With the purpose of systematically review decision rules to predict the patient's risk for active pulmonary TB at screening, Wisnivesky et al. analyzed studies that reported the sensitivity and specificity of clinical variables for predicting pulmonary TB. Sensitivity for identifying patients with active pulmonary TB ranged from 81% to 100%; specificity varied from 19% to 84%. It was observed that in most of the analyzed cases, results with higher sensitivity rates presented specificity lower or equal to 62% [23].

Many studies apply ANNs to support the diagnose of TB. Besides CART, Aguiar et al. also applied ANN models to predict pulmonary TB, reporting better results when describing, for example, a sensitivity of 100% and a specificity of 71%, considering HIV-negative patients [24]. To predict active pulmonary tuberculosis, El-Solh et al. used clinical and radiographic data, and the input data were constituted by 21 variables, such as age, diabetes mellitus, HIV, chest pain, emaciation, cough, fever, sweating, short of breath and radiographic variables. The authors reported a sensitivity of 100% and a specificity of 72% [25]. Er et al. also addressed TB diagnosis by modeling a neural network with two hidden layers using patient's epicrisis reports, which include 38 features [26]. Information about complaint of cough, chest pain, body temperature, dyspnea, weakness, sputum, smoking habit and laboratorial tests were included, achieving an accuracy of 93.93%. Genetic algorithm was applied by Elveren et al. to train a neural network with two hidden layers also based on patient's epicrisis reports, including results of preliminary examination and laboratory tests. An accuracy of 94.88% was measured [27]. Aiming at a non-invasive method of pleural tuberculosis diagnose, Seixas, et al., developed a neural network based on clinical history and HIV information of 137 patients, reporting an accuracy of over 90% [28].

There are few studies that evaluated screening approach for DR-TB and/or MDR-TB diagnoses [29,30]. Martinez et al. performed a combination of bivariate analyses and forward logistic regression model to develop a clinical prediction rule to stratify risk for MDR-TB among patients with pulmonary TB in Lima, Perú [29]. Variables were included according bivariate analysis and the dataset formed by clinical findings (prior TB, MDR-TB contact, abnormal lung exam) and one radiological pattern (cavity). Results reached sensitivity of 72.6% and specificity of 62.8%. Boonsarngsuk et al. retrospectively analyzed patients with culture-positive from respiratory specimens in Bangkok, Thailand [30]. Aiming to develop a diagnostic algorithm for newly-diagnosed TB patients, a score was created to discriminate patients among drug sensitive and drug-resistant TB. Variables were included according to its statistical significance in a multivariate logistic regression model, including: general demographical information, and Drug Susceptibility Testing (DST) and radiographical examinations, HIV status, underlying comorbid condition, history of previous TB disease and treatment, sputum acid fast bacilli (AFB) smear result, chest radiographical finding and DST results for each drug. The model reached a sensitivity of 57.7% and specificity of 67.8%.

The results from the literature indicate that neural networks models seem to present better performance in terms of sensitivity, when compared to other computational methods developed in

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