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TBM-App: a clinical decision support system for tuberculous meningitis

Luiz R A dos Santos*[a], Lívia M P Anselmo[a], Lucas S Oliveira[a], Fernanda S Merli[a], Carla C Silva[a], Gabriela C S Prado[a], Nathalia Y Crepaldi[a], Filipe A Bernardi[a], Matheus A Marçal[a], Antonio R-Netto[a], Rui P C L Rijo[a,b], Valdes R Bollela[a], Domingos Alves[a]

[a]Ribeirão Preto Medical School, University of São Paulo 14049-900, Ribeirão Preto, Brazil
[b]School of Technology and Management, Polytechnic Institute of Leiria, 2411-901, Leiria, Portugal

Abstract

Tuberculosis (TB) was responsible for approximately 1.6 million deaths in 2017 and it is the deadliest among the infectious diseases, killing more than Acquired Immunodeficiency Syndrome (AIDS) related diseases. One of the most lethal forms of this disease is the central nervous system TB. The clinical and microbiological diagnosis of tuberculous meningitis (TBM) is still a challenge and to standardize the diagnosis and offer more reliable information to the decision-making process in the clinical practice, predictive scores were created and adapted for the Brazilian context. The score implementation will require staff training but has the potential to reduce time to the TBM diagnosis and therefore start correct treatment early. Although, there is a need to increase the access to the score and to facilitate its use among physicians to save time and resources. This study shows the design and development of a multiplatform mobile application to calculate the predictive score for tuberculous meningitis, in order to support clinical decisions. The preliminary results have shown an effective and versatile App, available to a variety of devices and which can still be available in places with limited or no internet access.

* Corresponding author. Tel.: +55 11 94977-9407
E-mail address: luiz.ricardo.santos@usp.br

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1. Introduction

Technological applications in the health area, through biomedical informatics, result in important information for the prevention of diseases and management of healthcare in its different levels of complexity. These technologies increasingly evolve to reduce or eliminate medical errors by providing diagnosis to patients and to support decision-making and health information management [1].

Some challenges faced in the development and use of digital applications are related to the need to integrate data from the numerous information systems in the country and the uncertainty regarding the exposure of patients' data and conducts in the electronic databases [2]. All available information must be indispensable and relative to the work needs only. The health systems must comply with the norms of registration of patient care and guidelines regarding professional practice within each institution.

Health-related applications have brought the possibility of reducing costs by increasing efficiency in the management of care, optimizing health activities, especially in the hospital environment, as there is a growth in health spending and high rates of wastage of materials and technologies [3].

Medical diagnosis of diseases is one of the main areas in the healthcare assistance. One of the greatest challenges for health professionals is the large number of procedures a patient to be submitted to in a short amount of time, spending as little resources as possible to guarantee the effectiveness of care. Facing this scenario, technology has been a strong ally, helping health professionals to be more efficient at work [4].

In this article we will address a specific technology for medical assistance known as CDS – Clinical Decision Support. CDS systems ensures quick and accurate access to patient information during treatment and assists healthcare professionals in decision making, recommending procedures, and prescribing medication using data from diagnostic evidence.

Another important point to consider is that the volume of medical information is constantly growing through scientific evolution, with new medicines and new diagnostic tests, which makes updating professionals a necessary but complex task. The CDS plays a central role in this task, supporting the possibility of changing medical conducts that reflect in improvement in patient care and substantially helping professionals to make decisions with more assertiveness, efficiency and safety [5][6]. The disease chosen as the target and scenario for the development of this research was tuberculous meningitis, an infection of the meninges (membranes of the cerebral envelope and of the spinal cord), coming from complications of an untreated tuberculosis. In tuberculous meningitis, the bacteria leave the lung and spread to other organs of the body through the bloodstream. It can be fatal if not treated effectively and quickly. Data from the World Health Organization (WHO) estimate that more than 10 million new cases were reported in 2017, and TB deaths reached 1.6 million people, remaining the top 10 cause of death worldwide [7]. Although Tuberculous Meningitis presents on average 1% of all TB cases, it is disproportionately relevant, as it kills or disables around 50% of those infected [8].

The clinical diagnosis of tuberculous meningitis is still a challenge, and in order to standardize the diagnosis and offer a scientific basis to aid decision-making in clinical practice, predictive scores for tuberculous meningitis were created in Cape Town, South Africa [9]. Later this score was adapted for use in Brazil [10]. Despite the advances obtained with the standardization of predictive scores, there are no documented records of specific mobile applications for tuberculous meningitis, making the present research proposal unprecedented and extremely relevant in the scientific literature. This App has four defining criteria: clinical information based on history and physical examination, Cerebrospinal Fluid (CSF) Lab results, Central Nervous System (CNS) images and the evaluation of TB in other anatomic sites (lung, nodes, etc.). It considers all the relevant aspects and data required for the TBM cases in a single device, accessible to all the staff members, leading to a fast and more reliable diagnosis. We know that there are hospitals without access to all the medical technologies that may delay TBM diagnosis. This App encompasses all possible diagnosis of TBM, making it possible to refer the patient to large reference centers based on clinical findings, image and CSF laboratory information based on a study of Anselmo et al. (2017) [16] that evaluated 300 patients with suspected TBM in a retrospective study.

The literature has described, specifically for tuberculosis, that no matter how the treatment is conducted, in order to enhance adherence to TB medication, it is better to increase the involvement of patients with their health care; improve communication between health teams and provide patient-centered education and support during treatment [11]. Therefore, apps have a great potential to support TB prevention and treatment and also to help the patients to complete their healthcare [12]. It also helps clinicians to rule-out other important CNS infection that is part of TBM differential diagnosis.

The study of Alcantara et al. (2017) [14] emphasizes it is critical to minimize the reproductive rate of TB epidemic and reducing delay in diagnosis. The goal of the research was to reduce time for TB diagnosis through new machine learning and mobile health technologies. The authors proposed models based on deep convolutional neural networks and the results found pointed the approach as promising to improve TB diagnosis.

Another review study [13] has as purpose to identify and evaluate the functionalities of mobile apps focused on treatment and prevention of tuberculosis. The authors searched on three online app stores and considered only the apps focused on TB and in English, Spanish and Portuguese. Eleven functionalities were assessed for each analyzed app and searches were conducted to identify publications of testing of the available apps. They found 1332 relevant apps but only 24 of them met the inclusion criteria. Apps for TB treatment and prevention had minimal functionality and TB general information as guidelines and news or data collection. Some of the apps were developed for use by patients and none were developed to support TB patient management and involvement in their healthcare for example sending alerts and reminders. It was considered, as limiting factor for the potential of the apps, to facilitate patient-centered care. On the authors' evaluation refined works are necessary to be done in this area to support TB diagnosis and treatment.

Considering all the points described above and the motivation of this research, the objective of this work is the development of a multiplatform application that makes possible the calculation of the predictive score of tuberculous meningitis in clinical practice in order to support the medical decision.

The remainder of this paper is organized as follows: in the next section we present briefly the predictive score of tuberculous meningitis, the third section contains the detailed description of methodological steps and materials for the development of this research; section four contains the results and discussion of the development of TBM-app and, the final session presents the conclusion of the research and indicates possible future work to be developed on the subject.

2. The predictive score of tuberculous meningitis: the application core

Confirmation of the diagnosis of tuberculous meningitis remains a major challenge in a disease that is associated with high rates of morbidity and mortality in which early treatment can greatly improve outcomes. Bacilloscopy and culture, standards in the diagnosis of pulmonary tuberculosis, are very limited in tuberculous meningitis. Nucleic acid amplification tests (TAAN) represented a gain, however, up to a third of the cases are still not diagnosed by these techniques. Over time, many studies have used various case definitions for tuberculous meningitis, all based on clinical, laboratory, and radiological findings. Due to the difficulty of confirming the diagnosis, the cases are classified as probable, possible and those in which the diagnosis of tuberculous meningitis is excluded [15].

Diagnostic criteria and criteria for tuberculous meningitis had not yet been established and most studies used different definitions. In this context, in South Africa, year of 2009, 41 researchers created a consensus with criteria and definition for cases of Tuberculous Meningitis [14]. It takes into account the clinical presentation, examination of the Cerebrospinal Fluid (CSF), findings of Central Nervous System (CNS) images, microbiological exams in the CSF and molecular and confirmation of TB in other sites.

For the definition of cases, the authors propose a scoring system that includes:

- Clinical criteria (6 points maximum): duration of symptoms for more than 5 days (fever, stiff neck, vomiting); symptoms of tuberculosis (weight loss, night sweats, cough more than 2 weeks); recent history of tuberculosis contact or positive PPD; focal neurological deficit; paralysis of the cranial nerves; alteration of the level of consciousness.

- CSF criteria (4 points maximum): aspect of clear CSF; 10-500mm³ cell count; predominance of lymphocytes > 50%; protein concentration > 1g/l; CSF glucose (plasma) < 50% or CSF glucose <2.2 mmol / l.
- Image Criteria Computed Tomography (CT) or Magnetic Resonance (MRI) (6 points maximum): hydrocephalus findings, basal meningeal enhancement, tuberculoma, lacunar infarction, pre-contrast - basal hyperdensity.
- Criteria for tuberculosis in another site (4 points maximum): x-ray suggestive of active TB (signs of TB and miliary TB); CT/MRI or ultrasound outside the CNS; Identification of *M. tuberculosis* in culture (sputum, gastric lavage, pleural fluid, urine, etc); Positive PCR in samples outside the CNS.

The cases are classified as follows: probable case of tuberculous meningitis, score ≥ 12 points; if possible tuberculous meningitis, score of 6-11 points and absence of tuberculous meningitis (No TBM), score < 6 points.

In the study of Anselmo (2017) [16], the application of the score in 300 suspected cases of tuberculous meningitis, classified 40 probable cases, in which the score was greater than or equal to 11. The predictive score proved to be a powerful screening strategy for the diagnosis of TBM, being useful in confirming and excluding suspicious TBM cases. From these promising results, it was possible to develop and test an application that helps the physician in the calculation of this predictive score, for later decision making.

3. Materials and methods

For the team and project management we use the agile Scrum development methodology. One of the principles we use in Scrum is that each time cycle defined by the team (sprint), a functional increment of the system is implemented which gives focus to the project, increasing the speed of delivery of value and the project in general [17] [18]. The purpose of the meetings was to analyze what was done, what difficulties were faced by the team, and what would be the next steps in software development for the next sprint. The research methodology used was action research, which aggregates a set of different characteristics from the conventional experimental research and most of the qualitative methods. The main concepts of action research are:

- Cyclic - the steps are recurrent and follow a well-defined sequence;
- Participatory - all stakeholders actively participate in research;
- Qualitative and reflective, as it results in a critical analysis of its methods and outcomes at each stage of the cycle [19].

The software development technologies used were Bulma [20], for the responsiveness and styles of the application pages, for the development of business logic we use the JavaScript language through the Angular [21], a framework for multiplatform development (mobile and desktop) and, also, a *service worker* [22] was used: an application that uses persistent background processing and stays between the network and the browser to provide web applications even when the client device (mobile or desktop) is offline, basically, the service worker allows the application to be available via the browser even when there is no internet connection.

Intending provide security to patient data and according with General Data Protection Regulation (GDPR) [23] beyond the basic security level composed by login mechanisms organized in access levels, we adopted cryptography methods to limit access to data and to securely store and share information. The original data as a plain text form is transformed in illegible data called cipher text, which can be reverted to your original form using encryption and decryption algorithms.

4. Results and discussion

4.1. Development

A weekly meeting (sprint) was held with the team responsible for the software that has three undergraduate students of the biomedical informatics course and a software engineer. The key informants have a Physician MD. PhD, and a postdoctoral student in medical clinic.

There were many challenges during the development of this App. The first was to find an understandable language for the final users (physicians who work in the emergency room attending children and adults) and those with more generalist background who also see patients under investigation of tuberculosis and tuberculous meningitis. Another challenge, easily overcame, was the need to standardize the reference units from the international to the Brazilian standards for the Lab results, with the normal reference value.

During the pilot phase it was possible to detect that the screens without colors were confusing, and may lead to misinterpretation of the final score. For example, with the red color associated with poor outcomes and indicating the possibility of a treatment without final microbiological and/or molecular diagnosis of tuberculous meningitis. Another important improvement along the pilot study was the development of an "off-line" module to access and calculate the risk score. This was detected because in the University hospital there are some areas without good internet connection, and this might be the case of many different areas in Brazil where this App might be a useful tool.

4.2. The TBM-App

The Predictive Score for Tuberculous Meningitis (TBM-App) allows at each step, the physician fills the system with patient data according to each criterion presented: cerebrospinal fluid (CSF) criterion, MRI and/or computed tomography criterion, and evidence of TB in other sites criterion. At the end the result of the score is displayed. A system flowchart is shown in figure 1.

Fig. 1: system flowchart.

When filling the data in each of the criteria, the user can click on a checkbox corresponding to the attribute that the patient presents, then partial score obtained until that moment is shown. Figure 2. is an example of a system screen for one of the criteria (clinical criteria).

Each of the possible outcomes (probable, possible and unlikely) can be visualized on the last step, according to the patient's score. The colors of the warnings were based on the ANSI Z535.4-2011 standard that defines the red color for "danger" used in probable cases of tuberculous meningitis, the yellow color as "caution" used in the possible cases, and the green color for "safe" used in absence of tuberculous meningitis cases. By clicking on "more information" the user will be able to verify all the possible outcomes derived from the different scores of the score. For example, see Fig. 3.

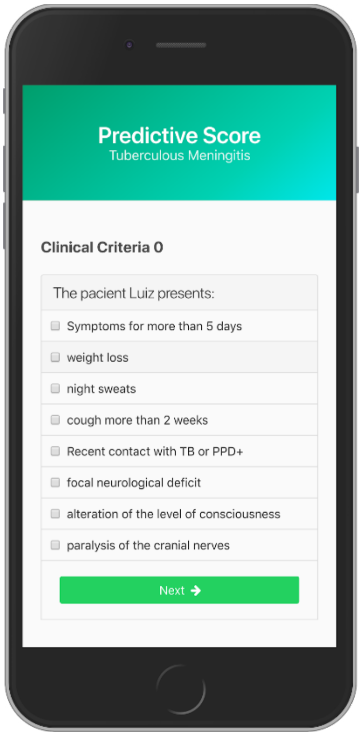

Fig. 2. example of a system screen for one criteria.

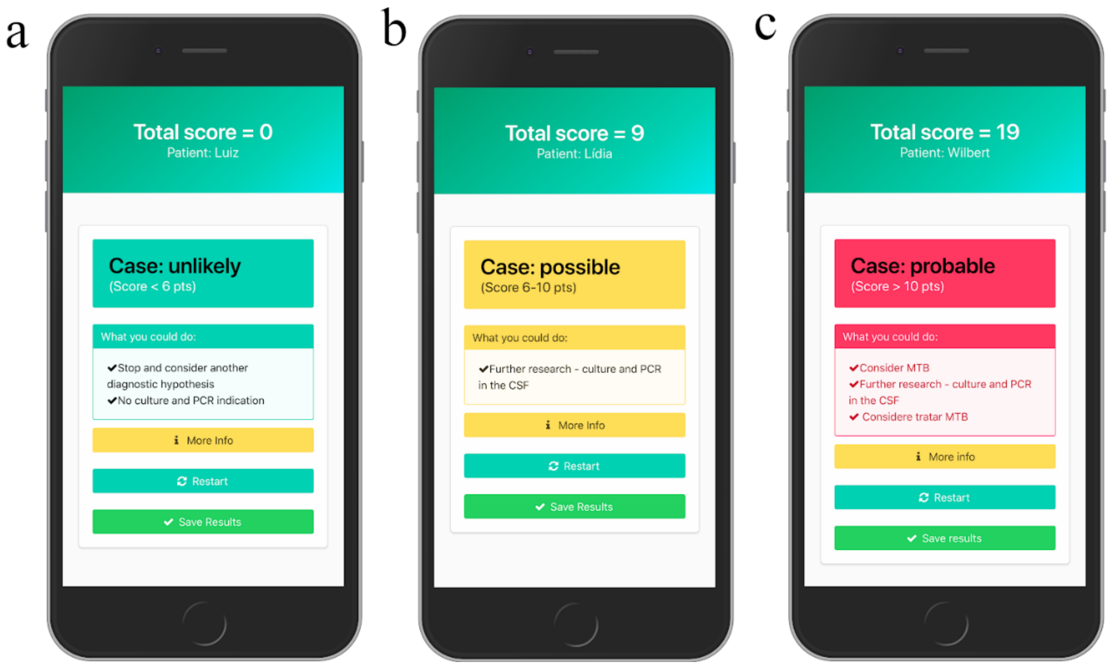

Fig. 3. (a) unlikely result; (b) possible result; (c) probable result

In the browser, when accessing the application site through a mobile device with Android operating system, the user may want to save the application on the home screen by doing so, because the technology of the service worker allows the application to be available offline. For desktop users, by detecting the lack of internet, the application automatically searches the service worker for offline operation, requiring no further user action.

4.3. Software/TBM-App Validation

By now, this App has been used in two major reference centers for TBM treatment in Brazil: 1. Clinics Hospital at *BLINDED - Site A*. (2013 to 2016); and 2. *BLINDED Site B.* (2018 and 2019). Medical reports referring to the use of the application in these two hospitals required great commitment from the hospital administration and decision makers to make TBM-App part of the institutional

protocols, in both centers.

On the other hand, the application had an excellent acceptance within the doctors, in *BLINDED - Site C.* TBM-App was used based on the patients´ records who had CSF sent to the TBM investigation. Of 94 CSF samples studied, it revealed that 60 (63.8%) were classified as possible, 6 (6.4%) as probable and 28 (29.8%) as non-TBM. From 10 confirmed TBM cases based on microbiological results, all were from the possible group. This lead to another review on the software and extra training for the users, and starting with pilot studies in more specialized areas (infectious and tropical diseases) which was enough to solve the problem.

At *Site A.* TBM-App in cell phone by infectious diseases specialists showed high acceptance in a prospective study to validate TBM-App clinical use after the retrospective study performed in this hospital from 2013 to 2019.

The diagnostic routine to confirm TBM in patients under clinical investigation tends to be easier, fast and more reliable with this App. There is an extra benefit when the score indicates non-TBM because it indicates with great certainty that other diseases, different from TBM, should be considered, as the low score is highly indicative of absence of CNS diseases caused by *Mycobacterium **tuberculosis***.

5. Conclusion and future works

We suggest that the application developed be incorporated into a context of electronic health record for the organized collection of diagnostic data, which will serve as a basis for improvement of the score, besides the incorporation of the score developed by Marais et al., (2010) [14]. In addition, a retrospective study to measure the software's ability to handle real-world cases is being conducted, and a second step is to carry out a clinical trial, where we can measure the effects of the intervention in environments with and without the application.

The application developed proved versatile because of the variety of devices for which it is available, and especially because it is possible to work in places with limited access or no internet access, besides being effective in calculating the proposed score. Therefore, the importance of studies like this is verified when we approach the clinical practice of the state of the art in science, incorporating teaching, research and extension.

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