PhD defence Lely del Rosario Solari Zerpa

Clinical Prediction rules to address diagnostic bottlenecks in tuberculosis

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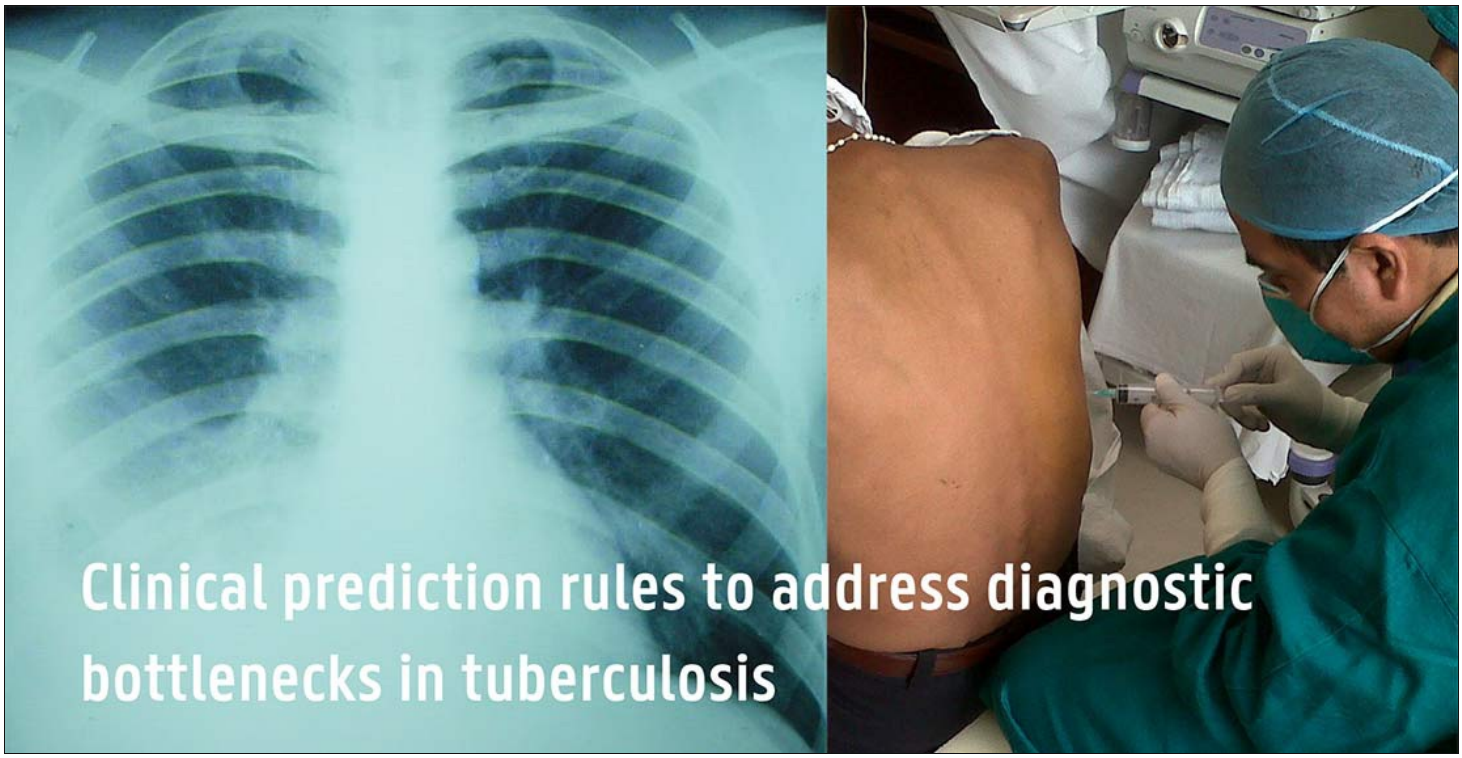

Dit is de omschrijving

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Summary:

Patients with suspected clinical pulmonary tuberculosis (PTB) and initially negative sputum smears should be adequately isolated when attending hospital emergency units, where they share spaces with other patients. Tuberculous meningitis (TM), the most severe clinical form of tuberculosis, becomes rapidly lethal and frequently results in neurologic sequelae due to protracted bacteriological diagnosis and delayed treatment. The pleura is another common site of extra-pulmonary tuberculosis. The diagnosis of tuberculous pleuritis (TP) relies on closed pleural biopsy, a risky, invasive procedure, which in resource-constrained settings is only available in tertiary hospitals. These three conditions represent diagnostic bottlenecks in tuberculosis.

Most of the disease burden they produce affects low and middle-income countries, such as Peru, where their prompt accurate diagnosis is problematic. New diagnostic tools for tuberculosis, based on molecular detection of mycobacterial nucleic acid, have been developed in recent years. However, they remain too complex or too costly for widespread use in local laboratories of these countries. Furthermore, it is unclear if these tests significantly contribute to better clinical outcomes, particularly with regard to the extra-pulmonary diagnostic bottlenecks described above.

Clinical guidelines are available, but operational limitations hamper their implementation, especially in resource-constrained settings. The Centers for Disease Control (CDC) guidelines on isolation of patients with suspected PTB are difficult to apply in high-incidence settings because of limited isolation space in local hospitals. Two available guidelines on TM, one developed by the British Infection Society Association and one by Marais, offer a well-structured approach. However, some discerning elements used in the former are hardly applicable in our setting (such as CNS imaging) or do not have discriminative power (such as identifying patients as high risk when originating from high endemic countries). The latter is intended for research rather than for clinical practice. Finally, no specific guidelines have been developed for the diagnosis of TP.

Clinical Prediction Rules (CPRs) could be useful for tackling these 3 bottlenecks in tuberculosis diagnosis and could also take account of the particularities of the most affected settings. A CPR is a "*prediction-making tool that includes three or more variables obtained from the history, physical examination, or simple diagnostic tests and that either provides the probability of an outcome or suggests a diagnostic or therapeutic course of action*" (Wasson,1985).

Our objectives with the current work were to identify existing CPRs that address each of these bottlenecks, if any, describe their characteristics and evaluate their performance in our setting, Lima, Peru, and to concurrently develop a "local" CPR.

Peru has a high tuberculosis incidence ($109/10^5$/ person year) and figures amongst the 20 countries with the highest number of multidrug resistant (MDR) cases. Out of 37,000 TB cases reported in 2016, 1200 were MDR and 80 extensively drug-resistant (XDR). 59% of all TB cases and 78% of MDR cases occur in the capital city, Lima. We conducted our research in 2 of the most important public hospitals in Lima: Hospital Nacional Hipolito Unanue and Hospital Nacional Cayetano Heredia. They are located in the north-eastern part of the city and cover its poorer districts, which are most affected by TB. We included in our different studies patients suspect for one of the three different aforementioned types of tuberculosis.

To develop local CPRs, we defined composite reference standards and the outcomes to be predicted and selected, based on the literature, the potential predictive findings to be evaluated. From here, we fitted multivariate models to derive the clinical scores. These scores were constructed by assigning to each withheld predictive finding points proportional to its odds ratio in the final multivariate models. An optimal cut-off point was defined (for extra-pulmonary tuberculosis, 2 cut-off points), to separate a positive from a negative range for predicting the disease (and an intermediate range in the case of TM and TP). We calculated the diagnostic indicators of sensitivity and specificity, likelihood ratios, predictive values and areas under the ROC curves against our reference standards. In addition, we performed bootstrap analysis to assess the internal validity of our local CPRs.

To identify standing CPRs for the 3 bottlenecks we used Ingui's procedures (Ingui, 2001) in our literature searches and we prioritized sensitivity. To evaluate the performance of the identified CPRs in our setting we followed a methodology similar to the one described above. After applying the CPRs to each of the patients in our corresponding suspect series, we calculated the standard diagnostic indicators against the reference standard.

The evaluation of existing CPRs for respiratory isolation of patients with suspected PTB showed that only Mylotte's attained a fair diagnostic accuracy in our setting. It had a 89% sensitivity, 69% specificity and an area under the ROC curve (AUC) of 0.91.

The local CPR we developed included the presence of miliary pattern, upper lobe infiltrate, cavities in the Chest X ray, weight loss, previous history of PTB and age as predictive findings. It attained a sensitivity of 93%, a specificity of 42% and an area under the ROC curve of 0.81.

On the topic of TM, we found that no CPR existed to differentiate between TM and all other conditions presenting as meningeal syndrome. Most CPRs have been developed to distinguish TM from bacterial meningitis, and a few others to distinguish TM from viral and fungal meningitides. Therefore, we first evaluated which cerebrospinal fluid (CSF) parameters were most relevant for the diagnosis of TM, according to the strength of their association with this outcome. Adenosine deaminase activity (ADA) had the best diagnostic performance (AUC 0.82), while glucose and protein in the CSF performed fairly (AUC 0.71 and 0.76, respectively).

Our locally derived CPR, which we subsequently developed, was the first one to draw a distinction between patients with TM and those presenting a wide range of other conditions with meningeal syndrome. It included adenosine deaminase ≥ 6 U/L in CSF, white cell count 10-500 in CSF and cough lasting 14 days or more, and had an AUC of 0.87.

Finally, we evaluated 12 CPRs for TP, 9 for TP diagnosis and 3 for distinguishing between TP and cancer. Neves' and Melo's CPRs attained a specificity of 100% in our setting, but their sensitivity was low (20% and 26%). In terms of overall accuracy, they performed far below ADA alone, which attained 87% accuracy.

The local CPR that we developed for diagnosing TP contained the following predictive findings: ADA, proteins in pleural fluid, age, lymphadenopathy, haemoptysis, disease duration, contact with a patient with tuberculosis and gender. This CPR attained 88% sensitivity and 92% specificity and an area under the ROC curve of 0.94. The overall accuracy was 89%.

Our studies show that Clinical Prediction Rules can be useful to address complex decision-making problems in tuberculosis management in high incidence low and middle-income countries. We identified useful existing CPRs to decide on respiratory isolation of PTB suspects in our emergency units and proposed a new, locally developed one. In the case of TM, we found that ADA is the most adequate single diagnostic laboratory parameter. We subsequently developed a local CPR for starting anti-tuberculous treatment in TM suspects. Finally, for PT, we identified existing CPRs that had high specificity but suboptimal overall accuracy in our context and we developed a local version that performed better

A limitation of our studies is the numbers of patients that could be included in the available time period. Even when our series constitute some of the largest in Latin America, the statistical power to assess the strength of a wide array of associations between predictive findings and the suspected condition was not always optimal. Another limitation is that implementation research and impact analysis were outside the scope of our work.

Our structured literature searches, on the other hand, guarantee thorough identification of existing CPRs for the three diagnostic bottlenecks addressed. Also, the use of patient information to evaluate several CPRs at the same time proves efficient and economical. Finally, with the locally developed CPRs we divide patients into high, intermediate and low likelihood categories according to whether or not they might have the form of tuberculosis under study, which offers an interesting, more comprehensive alternative than the usual dichotomic approaches.

None of the CPRs we developed has been adopted as of yet. However, the results of research on respiratory isolation contributed to a reformulation of the Peruvian tuberculosis programme's guidelines on managing tuberculosis suspects in emergency units and on securing within 2 hours the results of microscopic examination of sputum samples. The other 2 CPRs we developed have recently been published and have still to undergo knowledge translation.

Future research should concentrate on evaluating implementation strategies and quantifying the impact of the use of CPRs. Cost aspects, training approaches for users and the evaluation of the sustainability of their adoption should be investigated.

Our work provides evidence on the usefulness of CPRs for managing 3 diagnostic bottlenecks in patients with suspected tuberculosis. While CPRs can never replace clinical judgement, even experienced physicians will benefit from their use to better, more systematically handle these bottlenecks.