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Research Article

Tuberculous Pericarditis is Multibacillary and Bacterial Burden Drives High Mortality

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ABSTRACT

Background: Tuberculous pericarditis is considered to be a paucibacillary process; the large pericardial fluid accumulation is attributed to an inflammatory response to tuberculoproteins. Mortality rates are high. We investigated the role of clinical and microbial factors predictive of tuberculous pericarditis mortality using the artificial intelligence algorithm termed classification and regression tree (CART) analysis.

Methods: Patients were prospectively enrolled and followed in the *I*nvestigation of the *M*anagement of *P*ericarditis (IMPI) registry. Clinical and laboratory data of 70 patients with confirmed tuberculous pericarditis, including time-to-positive (TTP) cultures from pericardial fluid, were extracted and analyzed for mortality outcomes using CART. TTP was translated to $\log_{10}$ colony forming units (CFUs) per mL, and compared to that obtained from sputum in some of our patients.

Findings: Seventy patients with proven tuberculous pericarditis were enrolled. The median patient age was 35 (range: 20–71) years. The median, follow up was for 11.97 (range: 0·03–74.73) months. The median TTP for pericardial fluid cultures was 22 (range: 4–58) days or 3.91(range: 0·5–8·96) $\log_{10}$CFU/mL, which overlapped with the range of 3.24–7.42 $\log_{10}$CFU/mL encountered in sputum, a multi-bacillary disease. The overall mortality rate was 1.43 per 100 person-months. CART identified follow-up duration of 5·23 months on directly observed therapy, a CD4+ count of ≤199.5/mL, and TTP ≤ 14 days (bacillary load ≥ 5.53 $\log_{10}$ CFU/mL) as predictive of mortality. TTP interacted with follow-up duration in a non-linear fashion.

Interpretation: Patients with culture confirmed tuberculous pericarditis have a high bacillary burden, and this bacterial burden drives mortality. Thus proven tuberculosis pericarditis is not a paucibacillary disease. Moreover, the severe immunosuppression suggests limited inflammation. There is a need for the design of a highly bactericidal regimen for this condition.

1. Introduction

Tuberculous (TB) pericarditis accounts for 50–70% of pericardial disease in Africa (Mayosi et al., 2005, 2006, 2008). Mortality rates range between 17 and 60% (Mayosi et al., 2008; Pusch et al., 2014; Shaw et al., 2010). The *I*nvestigation of the *M*anagement of *P*ericarditis (IMPI) registry, a prospective observational study, revealed a case fatality rate of 26% within 6-months of diagnosis (Mayosi et al., 2008). Several host-factors were independent predictors of this early mortality, including the presence of HIV infection, increasing age, and concurrent pulmonary TB (Mayosi et al., 2008). However, these patients were followed up for only 6 months, and a definitive TB pericarditis diagnosis was confirmed in only 7% of patients. Thus, factors predictive of long-term outcomes in patients with proven TB pericarditis still need to be identified. Here, we identified factors predictive of long-term outcome using classification and regression tree (CART) analyses. We used CART because we did not want to use a model that pre-specified the important potential predictors. Instead we wanted a distribution- and assumption-free method to identify the predictors in the context of all potential clinical and laboratory factors. We also wanted to rank the predictors, in order to allow clinical decision making as to which factors to modify first to have the largest impact on reducing TB pericarditis mortality.

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TB pericarditis is considered to be a paucibacillary process, and the large pericardial fluid accumulation is attributed to an inflammatory response caused by a few tuberculoproteins (Cherian, 2004; Fowler, 1991). For that reason, the same regimen and doses used for pulmonary TB, and for the same duration, are administered to patients with extra-pulmonary TB including TB pericarditis (Mayosi et al., 2005, 2006, 2008, 2002; Pusch et al., 2014; Shaw et al., 2010; Cherian, 2004; Fowler, 1991). However, the baseline bacillary burden or temporal changes in bacillary load with therapy are yet to be rigorously quantified. These microbial factors are known to be important determinants of outcome in patients on the same type of standard therapy for pulmonary TB (Bowness et al., 2015; Diacon et al., 2010; Chigutsa et al., 2013, 2015). Here, we used the IMPI registry to investigate microbial, clinical, echocardiography and hemodynamic factors as possible predictors of long term death. Uniquely, we had an access to quantitative microbiology information based on liquid culture, which is known to better capture larger populations of *Mycobacterium tuberculosis* (*Mtb*) than solid agar techniques.

2. Methods

2.1. Study Setting and Study Design

The goal of the IMPI registry is to improve the outcomes of patients with TB pericarditis in resource-limited settings by improving access to clinical decision-making information (Mayosi et al., 2006). IMPI prospectively recruits patients with presumptive TB pericarditis from clinics across several African countries, collects and records observational data and then systematically analyzes these data to answer specific questions. We used the registry to investigate the role of several microbial and clinical factors as predictors of early and late mortality in patients with microbiologically proven TB pericarditis. We specifically focused on patients treated at Groote Schuur Hospital, a tertiary and teaching facility in Cape Town, South Africa, in order to control for uniformity of care, especially microbiology laboratory use and access. We examined study patients who had been treated at Groote Schuur Hospital between January 2006 and December 2010, and followed-up until January 1st 2012.

All patients received standard first-line anti-TB therapy recommended by the South African National Tuberculosis Program. Patients with prior TB history or retreatment were put on a longer regimen of the same first-line anti-TB drugs supplemented with streptomycin in the intensive phase. HIV-infected patients were treated with anti-retroviral drugs in line with local practice guidelines at the time (National Department of Health, 2004). (http://southafrica.usembassy.gov/media/2004-doh-art-guidelines.pdf) Progression of HIV and response to antiretroviral therapy was monitored using CD4 + T cell counts.

2.2. Definition of Terms

Pericardial constriction was defined using clinical and echocardiographic criteria described in the IMPI trial (Mayosi et al., 2014). The vital status of the patient (i.e. whether the patient was alive or dead by the censure date) was based on death certificate copies from the medical records and use of the eKapa and Clinicom databases, the Department of Home Affairs death records database and via verbal autopsy from family members. January 1st 2012 was set as the censure date.

2.3. Inclusion and Exclusion Criteria

The inclusion criteria for the IMPI registry is pericardial effusion confirmed via echocardiography in a patient with suspected TB (Mayosi et al., 2006). Patients with a presumptive diagnosis of tuberculous pericarditis and met eligibility for the IMPI registry also met study inclusion criteria. However, we excluded patients who did not have proven or definite tuberculous pericarditis for this sub-study of the IMPI registry. Additionally, only those patients who had pericardiocentesis within one week of diagnosis were included in this study. We included only patients who had been treated for 3 days or less with anti-TB antibiotics.

2.4. Modeling Bacillary Burden in Pericardial Fluid and Sputum

The standard laboratory measure of *Mtb* burden is colony-forming units per milliliter (CFU/mL); in sputum a smear grade is also used in clinical practice (Bowness et al., 2015; Diacon et al., 2010; Chigutsa et al., 2013, 2015; Epstein et al., 1998; Pfyffer et al., 1997; Giampaglia et al., 2007; Kolibab et al., 2014; Davies, 2010). Unfortunately, CFU/mL determinations are labor-intensive, time-consuming, require a biosafety level 3 facility, and at least 3 weeks of incubation. On the other hand, the mycobacterium growth indicator tube (MGIT) [Becton Dickinson Microbiology Systems, NJ, USA] liquid media system has become the standard in *Mtb* cultures for clinical specimens in South Africa (Diacon et al., 2010; Chigutsa et al., 2013, 2015). The MGIT reports a culture's time-to-positivity (TTP); the higher the bacillary load, the shorter the TTP (Epstein et al., 1998; Pfyffer et al., 1997; Giampaglia et al., 2007; Kolibab et al., 2014; Davies, 2010). Since TTP is highly correlated with CFU/mL, we utilized the TTP of pericardial cultures from 70 samples from the IMPI patients and a comparable randomly selected sputum samples from 18 patients with confirmed pulmonary TB from the South African TB reference laboratory in the Gauteng province, South Africa, to calculate the $\log_{10}$ CFU/mL. In the MGIT, a specimen without growth in over 60 days of incubation was considered negative for *Mtb* infection. Ziehl–Neelsen staining was used routinely to confirm positive MGIT results at Groote Schuur Hospital.

We used two approaches to translate TTP (in days) to CFU/mL, based on methods published in the literature (Bowness et al., 2015; Chigutsa et al., 2013, 2015; Davies, 2010). The first method is more conservative because it does not account for therapy received, has an r^2 of 0.998, and employs the following formula:

$$\log_{10}\mathrm{CFU/mL} = 2.6818e^{-0.046*\mathrm{TTP}}. \quad (1)$$

The second method is derived from the Gompertz model and was recently used by Bowness et al. (2015). This method accounts for bacterial decline during the first week of therapy. The formula is as follows:

$$\log_{10}\mathrm{CFU/mL} = \frac{\mathrm{TTP} - \left(562.318e^{-0.789e^{-0.195t}}\right)}{-64.111e^{1.002e^{-0.248t}}}, \quad (2)$$

where t denotes the days on therapy. The final pericardial fluid CFU/mL was adjusted for dilution made during sample preparation for each patient. Data extracted from the patients' notes did not indicate the number of days the patients was on therapy prior to pericardiocentesis. We assumed that most patients have the initial pericardiocentesis after receiving at least three days' worth of antibiotics (empirical anti-TB therapy is recommended for suspected pericardial TB by the national program). Given that we had excluded patients who received more than 3 days of therapy, we used the $t = 3$ for baseline $\log_{10}$CFU using this method.

2.5. Classification and Regression Tree Analysis

CART analysis is a machine-learning method that is distribution-free and can be used to assist in decision-making in the clinic (Breiman et al., 1984; Steinberg and Colla, 1995). CART analyses reveal trees that rank the important selected predictors and are akin to decision-making trees. Patients' demographic and clinical information including age, gender, HIV-infection, CD4 + T cell counts, receipt of anti-retroviral therapy, and history of active TB were examined using CART. Additional variables such as measures of hemodynamic stability (initial systolic, diastolic blood pressure and mean arterial pressure), heart rate, presence of pericardial constriction, receipt of pericardiectomy, and TTP derived