

**INVESTIGATION OF THE MANAGEMENT OF TUBERCULOUS
PERICARDITIS (IMPI) REGISTRY
SURVIVAL AND OUTCOMES SUB-STUDY**

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Abstract

Background: There is evidence that proven pulmonary and meningeal cases of tuberculosis (TB) are associated with a worse outcome than presumed cases.

Aim: To determine if survival is comparable for definite versus probable TB pericarditis among patients treated for TB pericarditis at the Groote Schuur Hospital (GSH).

Methods: A retrospective cohort study was conducted on newly diagnosed TB pericarditis cases referred to the GSH for pericardiocentesis from January 2006 to December 2010. Based on a folder review, baseline characteristics and laboratory findings were collected, and patients assigned as definite or probable TB pericarditis. A definite diagnosis was one in which pericardial fluid or tissue tested positive for *TB*, whilst a probable diagnosis was based on negative microbiological findings in the presence of clinical and indirect laboratory findings. The probable group was further divided into those with proven TB in another part of the body (except the heart) and those with probable TB.

Results: 192 patients that had a pericardiocentesis for suspected TB pericarditis were followed up for a median of 52.9 weeks (15.14 - 90.6). 93 (48.4%) of the patients had definite disease, 20 (10.4%) had probable disease with TB elsewhere and 79 (41.1%) had probable disease with no TB elsewhere; mortality was 19 (20.4%), 4 (20%) and 13 (16.5%), respectively over the follow-up period ($p = 0.799$). The predictors of mortality were low diastolic blood pressure, presence of cardiac tamponade and older age. The overall incidence rate of recurrent pericardial effusion was 47.1 cases per 1000 person-years; of constrictive pericarditis was 132.2 cases per 1000 person-years and of pericardiectomy was 34.4 cases per 1000 person-years. Allocation to probable or proven disease did not influence the outcome.

Conclusions: The survival and outcome of definite and probable TB pericarditis are the same. With attention to clinical parameters on admission, it is possible to determine which patients need more clinical care.

Key words: Survival outcomes. Definite and probable tuberculous pericarditis.

Dedication

To *J*, for closing one door so that I could walk into something better. I am forever indebted.

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Abbreviations

AAFB Acid-Alcohol Fast Bacilli

ADA Adenosine Deaminase

AIDS Acquired Immunodeficiency Syndrome

ART Anti-Retroviral Therapy

BPM Beats per Minute

CD4 Cluster of Differentiation 4

CI Confidence Interval

DOTS Directly Observed Treatment Short-Course

DNA Deoxyribonucleic Acid

GSH Groote Schuur Hospital

HIV Human Immunodeficiency Virus

IFN- γ Interferon Gamma

IMPI Investigation of the Management of Pericarditis

IQR Inter Quartile Range

mmHg Millimetres of Mercury

M. tuberculosis Mycobacterial Tuberculosis

PCR Polymerase Chain Reaction

RNA Ribonucleic Acid

TB Tuberculosis/ Tuberculous

PART A: PROTOCOL

THE INVESTIGATION OF THE MANAGEMENT OF PERICARDITIS (IMPI)

REGISTRY

SURVIVAL AND OUTCOMES SUB-STUDY

1.0 INTRODUCTION

Tuberculosis (TB) continues to rank amongst the leading causes of preventable disease in the developing world. In 2010, there were approximately 8.5 to 9.2 million cases of TB, and between 1.2 and 1.5 million deaths worldwide - 59% of these cases occurred in South East Asia and 26% in Africa, with continuing increases because of the human immunodeficiency virus (HIV) pandemic. ⁽¹⁾

The HIV pandemic has given rise to a changing epidemiology of TB and even more importantly, of extrapulmonary TB. In immunocompetent individuals, extrapulmonary TB constitutes between 15 to 20% of all TB cases, but this figure escalates to more than 50% in those who are HIV positive.⁽²⁾ HIV infection is thus associated with a rising incidence of all forms of extrapulmonary TB, including TB pericarditis.⁽³⁾

TB pericarditis carries a high mortality and morbidity, and it affects young people with a median age of 33 years. ⁽⁴⁾ If the condition accounts for 1 - 2% of all cases of TB, then about 500,000 to 1,000,000 individuals will be affected with TB pericarditis over the next 5 years.

⁽⁵⁻⁷⁾ The high burden of disease is reflected by the fact that TB pericarditis accounts for about 10% of patients hospitalized with heart failure in some parts of Africa⁽⁸⁾. In one series from the Western Cape Province of South Africa, TB pericarditis was responsible for 70% of cases referred with large pericardial effusion ⁽⁹⁾. In South Africa, at least half the patients with large pericardial effusions are co-infected with HIV ⁽⁹⁾

The diagnosis of definite/proven TB pericarditis rests on the finding of *Mycobacterium tuberculosis* (*M. tuberculosis*) in either pericardial fluid or tissue ⁽⁶⁾. The bacilli are demonstrated by staining and/or, positive culture in pericardial fluid, or the presence of caseating granulomata on histology of the pericardial tissue. Therefore, in order to prove TB pericarditis, pericardial fluid and/or tissue needs to be collected, usually via a diagnostic pericardiocentesis or pericardial biopsy. Generally *M.tuberculosis* yield in smears or in culture from body fluids, including pericardial fluid, is about 40-60% in endemic areas ⁽⁷⁾. To try and improve on this, molecular studies have been employed in the diagnosis of TB pericarditis. Specifically, nucleic acid amplification (NAA) techniques are now being tested to diagnose TB. ⁽¹⁰⁾⁽¹⁰⁾ These techniques amplify genomic deoxyribonucleic acid (DNA) or ribosomal ribonucleic acid (RNA) and use the signal to read out gene sequences. However, more commonly, the positive microbiology, histology, and polymerase chain reaction (PCR) of pericardial fluid are used to define patients with definite TB pericarditis.⁽⁹⁾

In areas of limited resources, diagnostic procedures and tests are not routinely performed and thus there is heavy reliance on indirect ways of determining pericardial TB disease status.⁽¹¹⁾⁽¹²⁾

It is the standard of care to commence anti-tuberculosis treatment before microbiological or histology results are available in countries where TB is endemic such as South Africa. ⁽⁹⁾⁽⁷⁾ A number of indirect tests or criteria are used to make a diagnosis of probable TB pericarditis, and in the absence of an alternative diagnosis, treatment is commenced. Probable TB pericarditis is considered to be the case when there is a pericardial effusion with either proven TB in another part of the body (except the heart) with positive microbiology, culture or histology results, or a lymphocytic pericardial exudate with elevated adenosine deaminase (ADA) levels ≥ 40 IU/l and/or a good response to anti-TB chemotherapy.⁽⁶⁾

Table1: Summarizing the definition of definite/proven and probable/presumed TB pericarditis*

| DEFINITE DISEASE | PROBABLE DISEASE |
|--|--|
| Isolation of tubercle bacilli in pericardial fluid in a stained smear or culture. | In presence of a pericardial effusion, evidence of tuberculosis elsewhere and/or |
| Histological demonstration of tubercle bacilli or caseating granulomata on pericardial tissue. | Lymphocytic pericardial exudate in presence of elevated ADA (≥ 40 IU/l) |
| - | Presence of pericardial effusion an appropriate response to a trial of anti-tuberculosis chemotherapy. |

* Mayosi et al 2005⁽⁶⁾

The adverse outcomes of TB pericarditis are well known and they include cardiac tamponade, recurrent pericardial effusion, constrictive pericarditis and death. ^(6,7,13-16)

The long-term impact of the classification of definite versus probable TB pericarditis on patient outcomes is, however, not known.

2.0 STUDY JUSTIFICATION

A retrospective study that sought to determine the high long term case fatality rate of patients with proven versus non-proven TB meningitis was reported in 2010. It showed 60% mortality in proven versus 15% in non-proven cases over 8.71 years. ⁽¹⁷⁾

A study conducted in India showed that the 18 month mortality in pulmonary TB was observed to be highest in patients with smear positive disease (34.7%) and lowest in patients in those with smear and culture negative disease (5%). ⁽¹⁸⁾ It is not known whether there are differences in survival in patients with proven TB pericarditis compared to those with probable disease.

A preliminary analysis to determine this difference was carried out on the 2006 Investigation of the Management of Pericarditis in Africa (IMPI) registry. It comprised 111 patients, out of which 12 had definite TB pericarditis. This analysis showed that when looking at the short-term outcomes, there was a trend towards higher mortality in patients with definite versus those with probable TB pericarditis. Aspiration of pericardial fluid was only performed in 26 (14.1%) patients thus limiting the ability to distinguish between definite and probable disease. ⁽⁴⁾

It is imperative to repeat this study in a larger population in whom the diagnosis can be verified by pericardiocentesis and determine not only the case fatality rate, but also the factors that would predict the profile of patients with poor outcomes that would possibly require more intensive care and follow up.

3.0 STUDY HYPOTHESIS

In patients with TB pericarditis, patients with definite disease have worse outcomes than those with probable disease despite receiving the same treatment.

4.0 OBJECTIVES

4.1 Primary Objective

- To compare overall survival between patients with definite and probable TB pericarditis.

4.2 Secondary Objective

4.2.1 To identify predictors of mortality in patients with probable and definite disease.

4.2.2 To determine the incidence rates of recurrent pericardial effusion requiring pericardiocentesis, constrictive pericarditis and pericardiectomy in patients with definite and probable TB pericarditis.

5.0 LITERATURE REVIEW

5.1 Epidemiology

TB remains a global health issue despite the availability of chemotherapy for more than 60 years. Before the HIV epidemic, 80% - 85% of reported TB cases were pulmonary in nature with the remaining 15% - 20% involving either extrapulmonary sites only or both pulmonary and extrapulmonary sites.⁽¹⁹⁾ There have been a rising number of reported extrapulmonary TB cases, with as many as 70% being associated with the HIV/AIDS pandemic.⁽²⁰⁾

The rise in the number of extrapulmonary cases has also included an increase in the number of TB pericarditis cases.⁽²⁾⁽³⁾ TB is associated with less than 5% of presenting cases of pericardial disease in the developed world, but remarkably causes between 50 and 70% of disease in the developing world.^{(3) (6,9,10)}

Before specific treatment was available, mortality from TB pericarditis was in excess of 80%, but with the roll out of anti-tuberculous chemotherapy, mortality declined to less than 10% by the 1980's.^(21,22) The advent of HIV-TB co-infection has, however, been associated with an increase in not only the incidence of extrapulmonary TB but also a rise in the mortality rates.^{(4) (23)} In TB pericarditis, mortality has been shown to range from 17% – 40%, with rates being highest in individuals with AIDS.^(4,8)

TB pericarditis continues to receive special attention because it is difficult to diagnose, has serious complications, and there exists a paucity of adequate evidence for its management especially in the era of HIV-TB co-infection.⁽⁴⁾

5.2 Diagnostic techniques

Making a definite diagnosis of TB pericarditis requires the identification of *M.tuberculosis* from either pericardial fluid or tissue. In the ideal situation, this would be done prior to commencing treatment. In most instances, however, treatment is commenced before culture results are available. The clinical decision to do this may be based solely on clinical signs and symptoms or indirect laboratory tests, especially in resource poor settings where diagnostic facilities may be limited. ^(9,24)

Microscopy remains the simplest and most widely used laboratory investigation for detecting *M.tuberculosis*. The fluid aspirate or tissue can be processed using the Ziehl-Neelsen stain in search of acid-alcohol fast bacilli (AAFB's). The sensitivity of these smears ranges from 10% - 42%. The process is limited by the need for at least 5 000 bacilli/millilitre to be present for AAFB's to be seen under the microscope. ^{(12) (6)}.

It is good practice to subject samples to both microscopy and culture. Culture remains the gold standard for confirming the diagnosis. It has a sensitivity that varies between 50% and 100%. ^(12,25). Pericardial tissue samples can also be processed histopathologically. This process has a sensitivity of 87% and specificity of 100%. It is less sensitive in patients with HIV given the spectrum of changes that may impede the formation of granulomata and cavitory disease. ⁽¹⁰⁾

The severe consequences of a delayed diagnosis have prompted research into techniques with improved diagnostic yield. These include nucleic acid analysis by PCR. The sensitivity and specificity of pericardial fluid samples subjected to PCR have proved disappointing at 30% and 100% respectively. ⁽¹⁰⁾ The sensitivity and specificity are better when tissue samples are used instead, but also have a higher yield of false positive results. ⁽³⁾

Adenine deaminase (ADA) enzyme assay is an important biomarker than can be used to strengthen the diagnosis of TB pericarditis in the absence of a direct method in TB endemic areas.⁽²⁵⁾ A systematic review evaluating the potential benefits of ADA as an adjunct to diagnosis in TB pericarditis showed that when 31 studies were compared, the sensitivity of the assay was 88% and its specificity 83%. It had an area under the curve of 0.954 showing a great corroboration as a diagnostic tool.⁽²⁶⁾ This result is further corroborated by the study by Reuter et al who found a sensitivity and specificity of 87% and 89% respectively in a TB endemic area.⁽⁹⁾ These test characteristics justify the use of ADA to strengthen the diagnosis in circumstances where bacilli cannot be isolated.

5.3 Complications of TB pericarditis

Cardiac tamponade: This life-threatening complication arises from the slow or rapid compression of the heart by excess amounts of fluid accumulating in the pericardial space.⁽²⁷⁾

As the volume of fluid increases in the pericardial space, the intrapericardial pressure rises. When the intrapericardial pressure equals the right atrial and diastolic right ventricular pressures, the transmural pressure approaches zero. This severely impedes cardiac inflow and may be fatal.⁽²⁷⁾⁽²⁸⁾ Symptoms include shortness of breath, palpitations, cough and chest pain with or without weight loss and night sweats. The clinical signs require a high index of suspicion and include tachypnea, tachycardia of ≥ 90 beats per minute, jugular venous distention, pulsus paradoxus >10 mmHg, hypotension and attenuated heart sounds.^{(7,29) (28)}

Treatment of tamponade involves aspirating the pericardial fluid by pericardiocentesis which should be done under the guidance of echocardiographic imaging or fluoroscopy.

Complications include pneumothorax, hemorrhage, embolism, perforation of the heart chambers, and laceration of the great vessels, infection and death. ⁽²⁹⁾

When present at diagnosis of TB pericarditis, cardiac tamponade is believed to indicate a late presentation and thus advanced disease. This may account for why it is also a predictive factor for the subsequent development of constrictive pericarditis.^(30,31) The association of tamponade with definite and probable TB pericarditis, and thus its role in mortality in the two groups is not known.

Recurrent effusion: In some cases, patients require repeat pericardial aspiration for recurrent effusion and tamponade. Effusions that require two or more invasive procedures for drainage are called recurrent pericardial effusions.⁽¹⁹⁾ Whilst they may occur in some patients with TB pericarditis, they may also signal other underlying disease such as malignancy, uraemia, aortic dissection and non-mycobacterial infection. Distinguishing between mycobacterial disease and malignancy can be difficult but needs to be ascertained as recurrent effusions in both are associated with a poor prognosis, especially when HIV-related ⁽³²⁾.

Constrictive pericarditis: Another important complication of TB pericarditis is constrictive pericarditis which generally develops within the first six of months of a patient's presentation with effusive pericarditis.^(7,15,22) It arises from the loss of the normal elasticity, and subsequent fibrosis of the pericardial sac. The fibrosis may be partial or global and causes a non-pliable pericardial sac. This results in impaired diastolic filling and dissociated intracardiac and intrathoracic pressures during respiration.

The patient may thus present with shortness of breath, palpitations, easy fatigability, abdominal swelling and abdominal pain (from hepatic congestion). On examination there may be raised jugular venous pressure, a sinus tachycardia with a low blood pressure and a pericardial knock - which corresponds with the sudden cessation of ventricular filling early in

diastole. There may also be pedal oedema and hepatomegaly due to hepatic congestion. If left untreated, constriction results in significant morbidity and eventually, mortality. ⁽⁴⁾

Pericardiectomy remains the treatment of choice for patients who develop symptomatic constrictive pericarditis. This procedure involves the surgical stripping of the parietal pericardium, either partially or completely. It helps to improve the patient's quality of life and is ideally performed in a well-equipped facility in the presence of surgical expertise. The procedure is associated with 6 – 12% mortality in the developed world. ⁽³³⁾

Death: Despite the availability of anti-TB treatment for more than 60 years, TB pericarditis still carries an unacceptably high mortality rate. ⁽⁴⁾ From the pre-chemotherapy era rates of greater than 80%, the number of deaths reduced to less than 10% in the early 1980's ⁽³⁴⁾, these figures have however increased over the past 20 years to between 17% and 40% with the advent of the HIV pandemic. ⁽⁴⁾ Patients receiving appropriate treatment have a variable course of recovery widely believed to be related to how early the disease is detected and when treatment is commenced. ⁽³⁵⁾

5.4 Factors associated with mortality in TB pericarditis

5.4.1 HIV infection

There have been different studies conducted to ascertain different aspects of the relationship between HIV and TB pericarditis. A study by Mayosi et al, showed that clinical immunosuppression raised mortality from 17% to 40%. ⁽⁴⁾ In the study by Hakim et al, it was shown that the use of anti-tuberculous therapy with steroids in HIV positive patients resulted in fewer deaths when compared to those with only anti-tuberculous treatment. ⁽³⁶⁾

5.4.3 Age

TB pericarditis can affect an individual at any age. In endemic areas, some series have shown that individuals in the third and fourth decades of life are most likely to develop the condition. ⁽¹⁴⁾ In a study on mortality in patients treated for tuberculous pericarditis, increasing age was a predictor of mortality. ⁽⁴⁾ The underlying reasons for this have not been determined.

5.4.4 New York Heart Association Class IV on admission

Another important feature was the presence of New York Heart Association Class IV symptoms at presentation. ⁽³¹⁾ It would appear that this was related to prolonged pre-treatment duration, and would suggest that the longer a patient remains untreated, the less likely they are to remain alive despite commencing treatment. These patients tended to suffer poorer outcomes as well as longer durations of hospital stay. ⁽³⁵⁾ Atrial fibrillation is self-limiting and harmless. ⁽³⁷⁾

5.4.5 Adjunctive corticosteroids

The role of corticosteroids in the management of TB pericarditis remains largely unresolved. A review of randomized controlled trials on the use of adjunctive steroids in the treatment of TB pericarditis showed that steroids could have beneficial effects on morbidity and mortality, but that the trials included were too small to be conclusive. They also did not have sufficient information regarding the role of adjunctive steroids in HIV- positive and HIV-negative. ⁽¹⁵⁾ The role of steroids is being re-evaluated in the light of HIV in a large multi-centre randomized controlled clinical trial. ^(22,24)

Summary

TB pericarditis is a serious extrapulmonary manifestation of tuberculosis. It is not easy to diagnose and it may present with severe complications that include cardiac tamponade, recurrent pericardial effusion, constrictive pericarditis and death. Factors which include age, HIV co-infection and cardiac tamponade at admission are known to influence outcome in patients admitted with the condition. Patients with proven meningeal and pulmonary TB appear to have worse outcomes than those with presumed disease. It is not known whether patients with proven TB pericarditis have a different outcome to those with probable disease.

6.0 METHODS

6.1 Study design

The study was a combined retrospective and prospective cohort study in which registry and file based data on all patients who had pericardiocentesis for pericardial effusion from January 2006 to December 2010 were examined.

6.2 Population and Sampling

The study was conducted at the Groote Schuur Hospital (GSH), Cape Town, Western Cape Province of South Africa. Patients who underwent pericardiocentesis for suspected TB pericarditis and were started on anti-TB treatment were enrolled. This included patients enrolled onto the IMPI Africa Pericarditis registry with suspected TB pericarditis.

Patients were enrolled consecutively and followed up. These patients had to be within the first seven days of commencing anti-tuberculous therapy, and were recruited into one of two categories – those fitting the criteria for being definite TB pericarditis and those falling into the probable TB pericarditis group.

Suspected TB pericarditis is defined as a patient presenting to the hospital with a clinical syndrome of pericardial disease which is suspected to be caused by TB on the basis of clinical and/or laboratory findings leading to the commencement of anti-TB treatment as per national protocol.^{(9) (38)}

Definite and probable TB pericarditis have been defined under the introduction section of this protocol and summarised in Table A.1

6.3 Data Collection

Information regarding patient demographics, clinical characteristics, laboratory results and treatments instituted was collected from in-patient hospital folders using a standardised data extraction form (appendix B). Where available, patient outcomes were also recorded from folders.

Where there was no outcome noted, patient files from referring clinics were traced, eKapa and Clinicom databases searched, and also efforts made to obtain death certificates from the Department of Home Affairs. The date of censure of follow-up was 1 January 2012.

6.4 Identification of participants

Enrolment was based on a follow-up of all patients who underwent pericardiocentesis during the study period at the GSH. Further, lists of all processed pericardial fluid specimens were obtained from the microbiology laboratory to ensure that no patients were missed, in addition to the records obtained from the catheterization laboratory. The aim was to enrol all the patients who underwent pericardiocentesis and were seen at the GSH between January 2006 and December 2010 with a suspected diagnosis of TB pericarditis.

6.5 INCLUSION AND EXCLUSION CRITERIA

6.5.1 Inclusion criteria.

- Pericardial effusion confirmed on echocardiography.
- Pericardiocentesis and/or pericardial biopsy performed, and
- Within 1 week of starting anti-TB treatment.

6.5.2 Exclusion criteria

- Pericardial disease from other causes, e.g., malignancy, penetrating chest trauma in the preceding 12 months or uremia at initial assessment.

6.6 Sample Size Calculation.

Sample size was not calculated as the study sought to assess the outcomes of all the patients who underwent pericardiocentesis and were commenced on anti-TB treatment between 1st of January 2006 and 31st December 2010, as per inclusion criteria.

6.7 Definitions of variables and outcomes

The main variables used included:

- Cardiac tamponade on admission as determined by the presence of a pulsus paradoxus >10 mmHg , tachycardia >90 bpm, raised jugular venous pressure >5 cm and an echocardiographically confirmed pericardial effusion with at least one of the following : i) swinging heart, ii) diastolic collapse of right ventricle, left atrium and/or left ventricle, iii) failure of inferior vena cava to collapse on inspiration and/ or iv) tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration).
- Pericardial fluid microscopy for acid-alcohol fast bacilli (AAFB) and culture for *M. tuberculosis*
- Pericardial histology to identify caseating granulomata and AAFB.
- Microscopy, culture or biopsy findings of TB from another part of the body.
- HIV serology test
- Atrial fibrillation on admission prior to pericardiocentesis as documented in the clinical record
- Diagnosis of constrictive pericarditis, the need for repeat pericardiocentesis or the need for pericardiectomy based on the diagnosis of the attending physician and documented in the clinical record.
- The vital status of the patient (alive or dead) based on death certificate or family information.

6.8 Field Management

The study was at GSH and information was obtained from the records department and cardiology and microbiology. Where records were incomplete, an attempt was made to trace files from the referring clinics and use the eKapa and Clinicom databases. We also made use of the Department of Home Affairs death records database.

6.9 Quality Control

6.9.1 Improvement of Validity

Where information was missing, referring clinics were contacted and an attempt made to verify information. Where information was completely unavailable, no assumptions were made.

6.9.2 Improvement of Reliability

Reliability was ensured by the use of a standardised data extraction tool, and the use of multiple sources of information for each patient.

6.9.3 Pilot Study

No pilot study was carried out as this was part of a larger on-going registry.

7.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS PLAN

The data was analysed using STATA version 11.1. Associations were explored using bivariate and multivariate associations prior to any further analysis. Data were expressed as median and interquartile ranges for continuous variables and counts with percentages for categorical variables. Comparisons between patient groups (definite TB pericarditis, probable TB pericarditis with TB in another part of the body (TB elsewhere) and probable TB pericarditis with no TB elsewhere) were performed using chi-squared or Fisher's exact tests based on the numbers of patients in each group.

7.1 Kaplan Meier survival curves were constructed to compare survival rates between patients with definite TB pericarditis, probable TB pericarditis with TB elsewhere and probable TB pericarditis with no TB elsewhere.

7.2 Cox proportional hazards regression was performed to identify the factors associated with mortality in patients with definite and probable disease.

7.3 Incidence rates were calculated using standardized morbidity ratios. This was based on the number of new cases of complications during a given time. The complications for which incidence were calculated were the incidence of recurrent pericardial effusion, constrictive pericarditis and pericardiectomy.

8.0 STUDY LIMITATIONS

This research was based on a folder review, and collected registry data, and thus the validity of the findings depended on the quality of the data collected by clinicians who did not have a standard way of recording or collecting the information required.

Not all patients provided national identity numbers or correct contact information on admission. For this reason, some patients did not have complete outcome records, or neither

could they be traced via the Home Affairs Death records registry. Foreign patients could not be traced via the Home Affairs death records limiting that as a tracing route.

9.0 ETHICS AND COMMUNICATIONS

All data were initially collected with patient identifiers for the sake of correct follow-up, however, confidentiality was maintained during the process of data collection. As this is a folder based review, written consent was not obtained from all the patients. After data collection, the patients were de-identified to ensure their confidentiality.

9.1 Potential Harms

There was no potential harm as a result of this folder review.

9.2 Potential Benefits

The results of this study will be used to inform the management of TB pericarditis and further research in the field. The results will be an important source of information on the risk stratification of patients diagnosed as either definite or probable TB pericarditis.

9.2 Results and Communications

The findings will be presented at local, national and international conferences. The main findings will be published, and efforts will be made to ensure that the findings influence clinical practice guidelines, where relevant.

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PART B: STRUCTURED LITERATURE REVIEW

1.0 INTRODUCTION

1.1 Objective

The main objective of this literature review is to summarize what is known about the determinants of survival in patients diagnosed with TB pericarditis with emphasis on definite and probable disease.

Studies describing the epidemiology and outcomes of this condition and highlighting the complications will be included. Finally, there will be a summary of the gaps in the information available regarding survival in TB pericarditis.

1.2 Search strategy

Studies on TB pericarditis were found by searching PubMed, CINAHL Plus with full text, Google Scholar and the Cochrane Library. Studies with relevant key terms in their titles were identified, abstracts read and then the full text article. They included any published study with information on mortality or survival outcomes. Additional studies were identified from reference lists of original articles, reviews and treatment guidelines. Both qualitative and quantitative studies were included if they were in alignment with the objectives of the literature review.

From PubMed, 76 hits were retrieved, The Cochrane library had one review article and 10 listed trials, and 7600 hits were found on Google Scholar. Starting from the Cochrane Library and then PubMed databases, studies with relevant key terms were identified. Additional articles were then retrieved from Google Scholar via reference lists of original articles, reviews and treatment guidelines. Articles were restricted to those written in or available as English translated versions on the used databases.

Search terms included “*mortality in tuberculous pericarditis*”, “*TB pericarditis/mortality*”, “*constrictive pericarditis*”, “*pericardial effusion*”, “*pericarditis tuberculous/complications*”, “*survival in tuberculous pericarditis,*” “*proven versus probable disease tuberculosis,*” “*definite tuberculous pericarditis,*” “*probable tuberculous pericarditis*”

1.3 Relevance of included studies.

This literature review is based on studies conducted in both the developing and developed world. It includes systematic reviews, randomized controlled trials, cohort studies, case-control studies and conference abstracts and text book material. Where relevant, studies conducted prior to the adoption of specific anti-TB chemotherapy are included.

Studies were selected to include those that described survival outcomes, predictors of mortality, disease progression, predictors of complications, comparison with other extrapulmonary TB outcomes, and also for relevant descriptions before and after the onset of the human immunodeficiency virus (HIV) pandemic.

Selected articles were thus from peer-reviewed journals, clear in their sampling techniques and had a clear study hypotheses related to the topic at hand.

Whilst case reports provide extensive descriptions on the recruited patients, they were excluded from this literature review due to the difficulty that arises from attempting to make generalizations to wider populations from them.

2.0 LITERATURE REVIEW ON FACTORS INFLUENCING SURVIVAL IN TUBERCULOUS PERICARDITIS

2.1 Disease epidemiology and description.

Few, if any, infectious diseases have caused as much morbidity and mortality in the world as has TB. In 2010, there were approximately 8.5 to 9.2 million cases of TB, and between 1.2 and 1.5 million deaths worldwide - 59% of these cases occurred in South East Asia and 26% in Africa.⁽¹⁾

The burden of TB which is primarily pulmonary in nature may also manifest with extrapulmonary disease including TB pericarditis. This is particularly important with the advent of the HIV/AIDS pandemic which is recognized as the most common risk factor associated with the development of extrapulmonary TB.⁽²⁾

TB accounts for 4% of the cases of pericardial disease in the developed world, but remarkably causes between 70% - 90% of the new cases in the developing world.⁽³⁻⁵⁾

Prior to the adoption of the current isoniazid and rifampicin-based drug regimes, TB pericarditis caused mortality in nearly all affected cases. The roll-out of treatment during the last century saw this figure decrease to approximately 10%. The advent of HIV-TB co-infection has resulted in a change in the epidemiology of TB pericarditis with recent studies showing up to 40% mortality at 6 months despite starting adequate treatment.⁽⁶⁾⁽⁷⁾⁽⁸⁾

TB pericarditis generally develops from the spread of *M.tuberculosis* bacilli from the mediastinal, peritracheal or peribronchial lymph nodes to the heart. Occasionally haematogenous spread occurs from primary TB infection.⁽⁹⁾

It is postulated that there are four pathophysiological stages of the disease: (1) a dry stage which is characterized by a fibrinous exudate, a high concentration of mycobacterial bacilli and early scattered granuloma formation. This stage is caused by a tuberculo-protein hypersensitivity reaction; (2) an effusive stage that is associated with a serosanguineous lymphocytic effusion; (3) an absorptive phase that is characterized by a granulomatous inflammation and caseous necrosis; and (4) the constrictive phase which results from the fibrosis of both the visceral and parietal pericardium. This encases the heart and may become calcified, thus compromising the normal function of the heart and resulting in constrictive pericarditis. ⁽⁹⁾

Symptoms of TB pericarditis are generally vague and non-specific. They arise from immune responses that are triggered by bacterial proteins as the bacilli penetrate the pericardium. Symptoms may include fever, night sweats, and malaise and weight loss. As the disease progresses, there is worsening shortness of breath, cough, palpitations and chest pain. ^{(10) (9)}

This literature review focuses mainly on the effusive presentation of the disease.

2.2 Factors associated with death

The description of a high mortality in patients treated for TB pericarditis has prompted this study of risk factors of poor outcome in TB pericarditis ⁽⁴⁾. Several factors are explored including certainty of diagnosis, HIV - TB coinfection, presence of cardiac tamponade, cardiovascular functional status, the presence of atrial fibrillation, age and gender.

2.2.1 Definite versus probable disease

An important aspect of pericardial disease caused by TB that has not received much attention is that of the influence of a definite or probable diagnosis on the survival of a patient diagnosed with effusive TB pericarditis.

A definitive diagnosis is centered on the isolation of the *M.tuberculosis* in pericardial fluid or a pericardial tissue specimen.⁽¹¹⁾ This sample is obtained either by pericardiocentesis and/or open drainage with pericardial biopsy. Pericardiocentesis is an invasive and potentially fatal procedure that is ideally performed under echocardiographic or fluoroscopic guidance. It is associated with complications such as myocardial perforation, air embolism, arrhythmias and pneumothorax.⁽¹¹⁾

Depending on the laboratory methods used to process the specimen, the diagnostic yields range from 30% to 76%.⁽¹²⁾ Aspirated fluid needs to be apportioned for various tests including microscopy, culture, biochemical analysis, cytology and PCR. It has been suggested that extrapulmonary samples of TB infection are frequently paucibacillary. Furthermore, they may contain inhibitors that undermine the sensitivity of nucleic acid amplification-based techniques.^(13,14) Pericardial tissue can also be tested for granuloma histologically, but even this is associated with a low yields, especially in HIV positive patients.⁽¹⁵⁾ .

The simplest test remains microscopy which needs a bacillary density > 5,000 bacilli/millilitre to yield a positive result. The procedure is user dependent and thus subject to human error including cross-contamination. It also cannot distinguish between *M.tuberculosis* and non-tubercular mycobacteria.⁽¹⁰⁾

The gold standard for detecting TB remains culture.⁽¹⁶⁾ According to Reuter et al, culture specimens which tend to have a sensitivity ranging from 74-95% in cavitary pulmonary disease, decline to a sensitivity of between 25% and 30% in extrapulmonary disease.⁽¹⁴⁾ In pericardiocentesis, the diagnostic range fluctuates between 30% and 76%. This means that a definite diagnosis is not always possible.⁽¹²⁾

In an endemic area where pericardiocentesis cannot easily be performed, a clinical diagnosis of TB pericarditis can be made on the basis of a prediction model that includes the following features: weight loss, night sweats, fever $>38^{\circ}\text{C}$, serum globulin $>40\text{g/l}$ and a leukocyte count <10 cells/liter in the presence of an echocardiographically confirmed pericardial effusion.

The diagnostic index allocates 1 point each to weight loss >10 kg and night sweats, 2 points to fever, and 3 points each to a raised serum globulin and a normal leukocyte count. A score of 6 or more is associated with 86% sensitivity and a 76% specificity to diagnose TB pericarditis. This prediction model, also called the Tygerberg score, is invaluable where facilities for safe pericardiocentesis are absent, or where the procedure is not indicated, and treatment needs to be started empirically. ⁽¹⁴⁾

The Tygerberg score is summarized as follows:

Table B.1: Showing Tygerberg index

| Clinical Variable on Admission | Point(s) | Score Weight |
|---|----------|--------------|
| Weight loss $>10\text{kg}$ | 1 | 0.13 |
| Fever $>38^{\circ}\text{C}$ | 2 | 0.17 |
| Night sweats | 1 | 0.09 |
| Serum globulin $>40\text{ g/l}$ | 3 | 0.33 |
| Blood leukocyte count $<10 \times 10^9$ | 3 | 0.28 |

Because the clinical features of TB pericarditis are not specific, attempts need to be made to improve confidence in the diagnosis in the absence of mycobacterial isolation. In circumstances where clinical suspicion of TB is high but fluid aspirate does not isolate any tubercle bacilli, indirect methods can be used to strengthen confidence in the diagnosis.

One of the most important indirect methods available is the use of adenosine deaminase (ADA) levels in pericardial fluid. A level in excess of 40 IU/L is a useful indicator of TB infection in the presence of clinical features. ADA has a sensitivity of 87% and a specificity of 89% for diagnosing TB pericarditis.⁽¹⁷⁾ Other factors like gamma interferon (IFN- γ) levels of ≥ 200 pg/L can also be used.

This means that while a diagnosis of definite disease depends on the isolation of mycobacteria from pericardial aspirate or tissue, a probable diagnosis will be presumed based on the isolation of mycobacteria elsewhere in a patient with otherwise unexplained pericarditis; and/or a lymphocytic pericardial exudate with high ADA or IFN- γ levels; and/or an appropriate response after a trial of therapy.⁽¹⁸⁾

Table B.2: Showing definite and probable definitions*

| DEFINITE DISEASE | PROBABLE DISEASE |
|--|--|
| Isolation of tubercle bacilli in pericardial fluid by microscopy, culture and PCR. | In presence of a pericardial effusion, proof of tuberculosis elsewhere and/or |
| Histological isolation of tubercle bacilli in pericardial tissue. | Elevated ADA ≥ 40 IU/l and/or predominant lymphocytic cells in aspirated pericardial fluid and/or |
| - | Presence of pericardial effusion, clinical features and/or an appropriate response to a trial of anti-tuberculosis chemotherapy. |

*⁽¹⁸⁾Based on Mayosi et al 2005.

Studies comparing definite and probable disease outcomes:

A study that compared survival outcomes in patients with definite and probable disease was conducted prior to the availability of isoniazid and rifampicin-based treatment regimens.

Based on culture results for tubercle bacilli isolation, it showed a higher mortality in patients with proven versus non proven TB pericarditis, (83% versus 6% respectively). The investigators concluded that in cases where bacilli were easily detectable from pericardial fluid, prognosis was grave.⁽¹⁹⁾

A study by Colebunders et al, showed that patients who had negative smears but positive culture results had minimal disease with low bacillary counts. Mortality was also lower in this group of patients. The investigators thus inferred that infectivity and mortality in smear negative disease is lower, and consequently, less intense chemotherapy is needed to treat the condition.⁽²⁰⁾ This finding was supported by a trial in Indian patients which showed that mortality at 18 months was highest in those with positive smears (34.7%) and lowest in those who were both smear and culture negative (5%).⁽²¹⁾

Additionally, a retrospective study on mortality in patients treated for meningeal TB showed that there was a higher long term mortality in patients with proven meningeal tuberculosis as compared to those with non-proven disease (78% and 38% respectively).⁽²²⁾ This study followed up patients for a maximum of 8.71 years and the findings raised the question that perhaps management strategies for patients with proven disease may require revision. There have been no studies of a similar nature to compare survival outcomes in patients with proven and presumed TB pericarditis.

The outcomes noted in the pulmonary TB and meningeal TB patients did not establish whether the bacillary densities in patients with proven versus presumed disease were different. The studies did however raise questions about the adequacy of patient monitoring, drug dosing and treatment responses for proven versus probable disease. They also raised the

possibility of these findings being possible across all forms of TB, including TB pericarditis.

(23)

2.3.2 HIV-TB co-infection

In developing countries where TB is endemic, it is the sentinel disease for HIV infection.⁽²⁴⁾

Patients with both TB and HIV disease have been shown to present with fewer detectable AAFB's in their sputum and less frequent pulmonary cavitory lesions than HIV negative patients of similar demographics. HIV is also associated with more frequent extrapulmonary disease.⁽²⁵⁾

A study by Reuter et al, showed that the stage of immunodeficiency, the risk of disseminated TB and other serious opportunistic infections and ultimately death, all correlated with absolute CD4+ lymphocyte cell counts. Outcomes were evidently better in patients with counts >200 cells/ μ l. Only 25% of these cases appeared to have proven TB elsewhere in the body.⁽²⁶⁾ This meant that in the majority of patients, disease only involved the pericardium. This study was important because it was conducted in HIV positive patients that had no access to anti-retroviral treatment and so it helped to shed light on the clinical evolution of TB pericarditis in different stages of HIV disease.⁽²⁷⁾ An earlier study by the same authors also showed that a history of previous TB occurred less frequently in HIV positive patients and did not seem to influence the development of constrictive pericarditis or even predict mortality.⁽¹¹⁾

An observational study that described mortality in patients treated for TB pericarditis in Sub-Saharan Africa showed that the mortality in patients with AIDS was 40% at 6 months, and 17% for those without HIV at the same duration of follow up. In this study,

pericardiocentesis was only performed in 14.1% of the participants and a definite diagnosis established in 7.3%. The independent predictors of mortality in this study were increasing age, AIDS, pulmonary TB, proven non-TB pericarditis and use of anti-retroviral drugs. They also showed a decrease in mortality amongst those who underwent pericardiocentesis.⁽⁸⁾

2.3.3 Age and gender

TB pericarditis can affect an individual at any age. In endemic areas, various studies have shown the second, third and fourth decades of life to be the most likely to develop the condition.^(18,28) In a study on mortality in patients treated for TB pericarditis, increasing age was a predictor of mortality.⁽⁴⁾ Increasing age has also been shown to be a predictor of higher morbidity and mortality after pericardiectomy, thus increasing the overall mortality from TB pericarditis.⁽²⁹⁾

Various studies have shown that the proportion of males to females affected by TB pericarditis differs from region to region. Proportions range from a male: female ratio of 2.7:1, 1:1 and 1:3.⁽³⁰⁾ Local studies have also shown contrasting results on mortality when compared by gender. One study showed that poor black women were more likely to present with, and die from TB pericarditis, than men of the same racial and economic background.⁽¹⁴⁾ Whilst another study showed that mortality was higher in men than in women when controlling for age.⁽⁴⁾ These results point to the importance of following up all patients without respect for gender.

2.3.4 Adjunctive corticosteroids

A systematic review on the role of steroids in addition to anti-TB drugs in the treatment of TB pericarditis showed that the role of steroids remains largely unproven.⁽³¹⁾ The studies included in the review showed a reduced case-fatality rate and a favourable clinical outcome at 18-24 months of follow-up. The authors concluded that the findings were statistically inconclusive because of the low number of patients included in the review.⁽³¹⁾

There have been trials conducted in an attempt to investigate this role both prior to the HIV pandemic and after its onset.

Prior to the HIV pandemic, adjunctive corticosteroids showed favourable outcomes when received in combination with the recommended TB chemotherapy. Strang et al., showed that long term survival was better in those who had received steroids than in those who had not (94% and 85% respectively). The steroid-receiving arm of the trial also had fewer cases that required pericardiectomy as opposed to the placebo arm (21% and 30% respectively), thereby reducing overall morbidity as well. Long term mortality was however not affected in these patients.^(6,32,33)

With the onset of the HIV pandemic, a double blinded randomized trial in HIV positive patients with TB pericarditis was conducted to evaluate the role of steroids in addition to TB treatment. In this trial, Hakim et al showed that mortality was significantly lower in the steroid arm of the trial. This reduction was accompanied by lower morbidity levels in the same study arm. The recommendation of the investigators was for the inclusion of steroids to TB pericarditis treatment regimens.⁽⁷⁾ The gains of the study are yet to be confirmed in a larger randomized controlled trial.

2.3.5 New York Heart Association functional class and atrial fibrillation at presentation

A study on the predictors of constrictive pericarditis showed that patients who presented in New York Heart Association stage IV with features of right-sided heart failure including pedal edema, ascites and hepatic congestion, were more likely to progress to a constrictive stage and more at risk to die from TB pericarditis.⁽³⁴⁾ This is thought to be because the patients may already be in an effusive constrictive stage of the disease as opposed to a purely effusive stage. On pericardiocentesis, the symptoms would initially be relieved; however, irreversible changes would have already been set in motion. There is presently no known medical treatment for this stage of the disease.

Atrial fibrillation is common in patients with TB pericarditis. A prospective trial investigating its prevalence and natural history in patients with TB pericarditis was recently conducted. It showed that fibrillation was present in 25% of those enrolled and by the end of the follow-up period there was no significant association between atrial fibrillation and mortality. The investigators concluded that the atrial fibrillation in these patients was secondary to inflammatory processes caused by the underlying disease and as such, treatment of the disease resolved its presence.⁽³⁵⁾

These findings are in contrast to previous studies conducted in the Transkei by Strang et al in which atrial fibrillation was shown to be present in less than 3% of the studied population.⁽⁶⁾

2.3 Complications of TB pericarditis that may be associated with outcome.

2.3.1 Cardiac tamponade

Cardiac tamponade is an early complication of TB pericarditis. It is a life-threatening condition that arises from the compression of the heart by excess amounts of fluid accumulating in the pericardial space.⁽³⁶⁾ As accumulation continues, the pericardial pressure

becomes elevated throughout the cardiac cycle, and diastolic filling is therefore compromised.

The clinical signs include tachycardia of ≥ 90 beats per minute, pulsus paradoxus of ≥ 10 mmHg, hypotension and attenuated heart sounds. ⁽¹⁰⁾

Cardiac tamponade may be the presenting feature of TB pericarditis.⁽³⁷⁾ In different studies, it has been shown to be present at admission in 60% - 90% of patients at admission. ⁽³⁶⁾ ⁽³⁷⁾In a series by Suwan et al., tamponade on admission was a predictive factor for the subsequent development of constrictive pericarditis.^(34,38) This was not confirmed in a study by Hakim et al who showed that tamponade does not always predict progression to constriction as the majority of the patients enrolled in their study presented with tamponade, but none went on to develop constriction.⁽³⁹⁾ Neither study investigated an association between tamponade and mortality.

2.3.2 Recurrent pericardial effusion

In a proportion of TB pericarditis patients, recurrent pericardial effusions occur. These are defined as effusions that require two or more invasive procedures for drainage.⁽⁴⁰⁾ Whilst they may occur in some patients with TB pericarditis, they may also signal other underlying disease such as malignancy, uraemia, aortic dissection and non-mycobacterial infection. Distinguishing between mycobacterial disease and malignancy can be difficult but needs to be ascertained as recurrent effusions in both are associated with a poor prognosis, especially when HIV-associated ⁽⁴¹⁾.

2.3.3 Constrictive pericarditis

One of the most important complications of TB pericarditis is constrictive pericarditis. This condition is characterized by the inflammation, thickening and eventual fibrosis of the visceral and parietal layers of the pericardium. The fibrosis may be global or partial, and

results in the limitation of diastolic ventricular filling. As the scar shrinks, further compression of the heart occurs especially around the right side of the heart and around the great veins. The resulting signs and symptoms produced are due to systemic venous congestion. ⁽⁵⁾

In developing countries with a high prevalence of TB, constrictive pericarditis is considered to be of tuberculous etiology until proven otherwise. ^{(42) (6,8)} Early studies suggested that the early institution of medical therapy was associated with lower constriction and death rates, ⁽⁴³⁾ but it is now shown that between 4% and 50% of cases go on to die from constriction related complications, making constriction worth preventing regardless of etiology. ⁽⁴⁴⁾

Unfortunately, pericardial constriction may be the first presentation of TB pericarditis with no apparent symptoms to suggest a previous effusive stage. ⁽⁴⁵⁾

Pericardiectomy remains the treatment of choice for patients who develop symptomatic constrictive pericarditis. This procedure involves the surgical stripping of the parietal pericardium. The stripping may be partial or complete. It helps to improve the patient's quality of life but needs to be performed in a well-equipped facility under surgical expertise. It is associated with 6 – 12% mortality in the developed world. ⁽⁴²⁾ Pericardiectomy is also important for the high morbidity it is associated with. According to a nation-wide American series, morbidity was 48% post-pericardiectomy. ⁽⁴⁶⁾

Conclusion

The literature has shown that TB pericarditis is a serious and potentially fatal extrapulmonary manifestation of tuberculosis. The condition is not easy to diagnose and it may present with severe complications that include cardiac tamponade, constrictive pericarditis, recurrent

pericardial effusions and death. Several factors including age, gender, HIV co-infection, cardiac tamponade at admission and adjunctive steroid use are known to influence the outcomes in patients admitted with the condition.

There is also evidence that culture positive or proven pulmonary and meningeal TB may be associated with a worse outcome than culture negative or presumed disease. To the best of my knowledge, no information exists regarding the relationship between proven and presumed status of diagnosis and outcome in TB pericarditis.

I have embarked on a prospective observational study in the IMPI registry to test whether proven TB pericarditis has a worse outcome than probable TB pericarditis.

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PART C: JOURNAL MANUSCRIPT

South African Medical Journal

**INVESTIGATION OF THE MANAGEMENT OF TUBERCULOUS
PERICARDITIS (IMPI) REGISTRY
SURVIVAL AND OUTCOMES SUB-STUDY**

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Abstract

Background: There is evidence that proven pulmonary and meningeal cases of tuberculosis (TB) are associated with a worse outcome than presumed cases.

Aim: To determine if survival is comparable for definite versus probable TB pericarditis among patients treated for TB pericarditis at the Groote Schuur Hospital (GSH).

Methods: A retrospective cohort study was conducted on newly diagnosed TB pericarditis cases referred to the GSH for pericardiocentesis from January 2006 to December 2010. Based on a folder review, baseline characteristics and laboratory findings were collected, and patients assigned as definite or probable TB pericarditis. A definite diagnosis was one in which pericardial fluid or tissue tested positive for *TB*, whilst a probable diagnosis was based on negative microbiological findings in the presence of clinical and indirect laboratory findings. The probable group was further divided into those with proven TB in another part of the body (except the heart) and those with probable TB.

Results: 192 patients that had a pericardiocentesis for suspected TB pericarditis were followed up for a median of 52.9 weeks (15.14 - 90.6). 93 (48.4%) of the patients had definite disease, 20 (10.4%) had probable disease with TB elsewhere and 79 (41.1%) had probable disease with no TB elsewhere; mortality was 19 (20.4%), 4 (20%) and 13 (16.5%), respectively over the follow-up period ($p = 0.799$). The predictors of mortality were low diastolic blood pressure, presence of cardiac tamponade and older age. The overall incidence rate of recurrent pericardial effusion was 47.1 cases per 1000 person-years; of constrictive pericarditis was 132.2 cases per 1000 person-years and of pericardiectomy was 34.4 cases per 1000 person-years. Allocation to probable or proven disease did not influence the outcome.

Conclusions: The survival and outcome of definite and probable TB pericarditis are the same. With attention to clinical parameters on admission, it is possible to determine which patients need more clinical care.

Key words: Survival outcomes. Definite and probable tuberculous pericarditis.

***Supplementary results are attached as appendix A. This is a variation from the journal requirements**

Introduction

More than 100 years after the identification of *Mycobacterium tuberculosis* (*M. tuberculosis*) by Robert Koch, TB remains a global health problem, disproportionately affecting the developing world. TB pericarditis is an important extrapulmonary manifestation of TB that is associated with a significant level of morbidity and mortality. ^(1,2).

We aimed to determine if patients with definite TB pericarditis suffered worse outcomes than those with probable disease despite receiving the same treatment.

Methods

The study was a retrospective cohort study in which files of all patients who underwent pericardial aspiration for suspected TB were reviewed. It was conducted at the GSH, Western Cape, South Africa. Folders were selected for review if aspiration occurred between January 1 2006 and December 31 2010. Inclusion into the study was based on the patient being within their first week of TB treatment and having had a pericardiocentesis and/or pericardial biopsy performed in the presence of a confirmed effusion for suspected TB pericarditis. They were excluded if they had pericardial disease from any other cause such as malignancy or uremia, or were within one year of having experienced penetrating chest trauma.

Baseline characteristics of the patients and any subsequent procedures such as pericardiectomy were collected from folders. Patients were classified as definite TB pericarditis, probable TB pericarditis with proven TB elsewhere in the body or probable TB with no proven TB elsewhere in the body, depending on laboratory results. Definite TB pericarditis is characterised by isolation of tubercle bacilli from pericardial fluid or tissue by microscopy, culture or polymerase chain reaction (PCR). Probable TB pericarditis is based on the presence of a pericardial effusion with proof of TB elsewhere in the body and/or

adenosine deaminase (ADA) ≥ 40 IU/L and/or a predominantly raised lymphocyte count in the pericardial fluid, and/or an appropriate response to TB chemotherapy. ⁽³⁾

All patients were managed at primary care facilities from where they received TB treatment as per national guidelines ⁽⁴⁾. They were also commenced on anti-retroviral therapy (ART) at the discretion of their primary care physicians. They were referred back to the GSH in the event that they developed symptomatic constriction or needed pericardiectomy. Details on patient mortality or subsequent outcome were collected from patient folders, the Clinicom electronic database, patient tracing and the Home Affairs death records. All patients without any outcome despite attempts at tracing were excluded from the analysis. All patients were censored for follow-up on 1 January 2012.

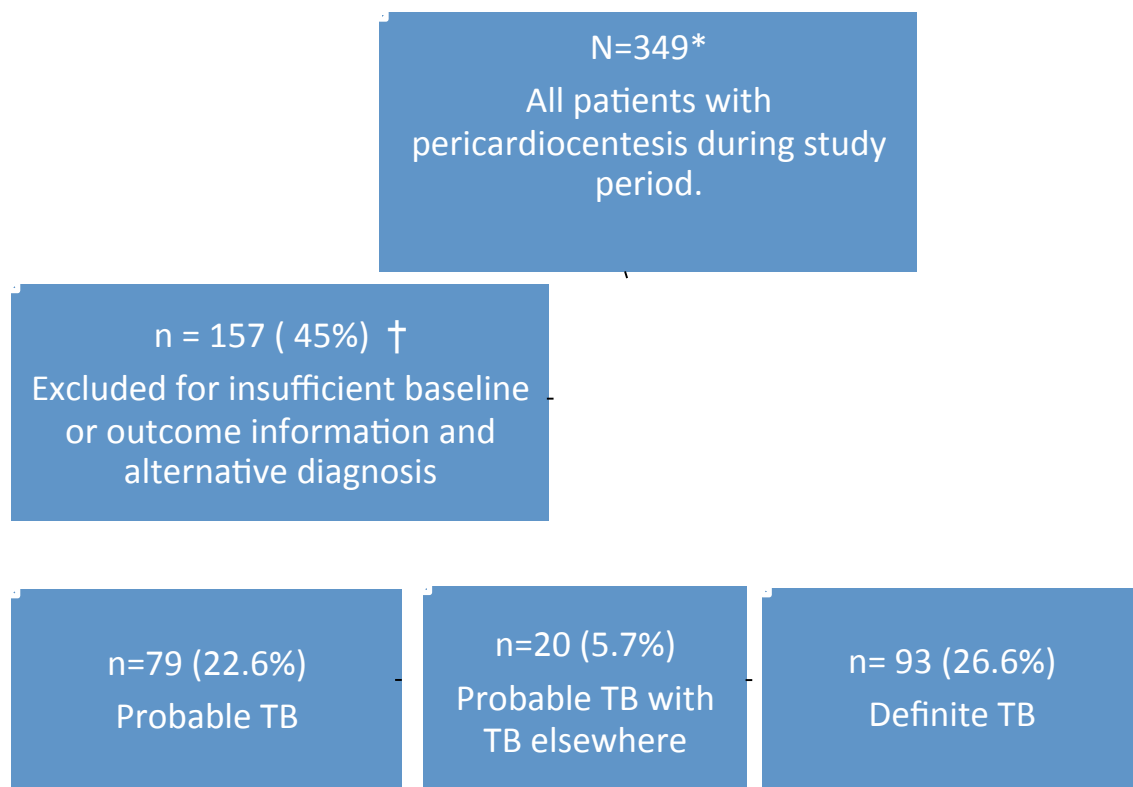
Retrieved patient data was recorded on a standardized form. All data was analysed using STATA 11.1. Associations of variables were made with chi-square tests and Fishers exact measurements where appropriate to compare characteristics between the three groups of patients. For the survival analysis, Kaplan-Meier curves were used and Cox proportional hazards regression used to determine predictors of mortality in the study population.

Incidence rates were calculated as the number of new cases of complications during a period of time divided by the person-time at risk. The research was approved under the Human and Research Ethics Committee of the University of Cape Town (HREC) 032/2009.

Results

During the study period, a total of 349 patients were identified to have undergone pericardiocentesis. Of this total 157 (45%) were excluded due to incomplete data baseline or outcome data. In the remaining 192 patients (55%), 93 (26.6%) were classified as definite TB pericarditis, 20 (5.7%) as probable TB with proven TB elsewhere in the body (except the heart) and 79 (22.6%) as probable TB pericarditis with no TB elsewhere.

Figure 1. Describing cohort of selected patients



*Included patients who met criteria for recruitment.

† included missing folders, patients that could not be traced due to insufficient follow-up information. 14 patients were excluded for an alternative diagnosis.

Table 1. 'Baseline characteristics of the study participants'

| RISK FACTOR | Definite TB pericarditis n=93 | Probable with TB elsewhere n= 20 | Probable with no TB elsewhere n= 79 | p-value |
|--|--------------------------------------|---|--|----------------|
| Age (years), median (IQR) | 34 (30-45) | 30 (24.5-37) | 30 (26-41) | 0.020 |
| Sex: Male, n (%) | 57 (61.3) | 10 (50) | 40 (50.6) | 0.322 |
| Clinical Features | | | | |
| Duration* (days), median (IQR) | 28 (14-31) | 24 (14-38.5) | 23 (14-42) | 0.692 |
| Pulse (bpm), median (IQR) | 114 (101-126) | 120 (99-120) | 110 (96-122) | 0.180 |
| Systolic BP, median (IQR) | 108 (97-114) | 100.5 (99-108) | 105 (96-117) | 0.823 |
| Diastolic BP, median (IQR) | 70 (64-80) | 72.5 (61-80) | 70 (60-80) | 0.670 |
| Pulse pressure, median (IQR) | 37.5 (30-42) | 34.5(22-42.5) | 36 (30-45) | 0.586 |
| Mean arterial pressure, median (IQR) | 70 (60-80) | 85.9 (75.2-90) | 80.4 (73– 91) | 0.657 |
| §Atrial Fibrillation, (n=124) (%) | 15 (55.6) | 1 (5.0) | 8 (10.4) | 0.238+ |
| ¶Tamponade (n=184) (%) | 46 (52.9) | 7 (35.0) | 29 (37.7) | 0.380+ |
| Laboratory features | | | | |
| ADA (IU/L) median (IQR) | 73 (52.7-99) | 75.3 (42.4-121) | 55 (30-81.9) | 0.025 |
| Globulin (gm/l), median (IQR) | 54.5 (47.6-63) | 46.5 (44-58) | 48 (43 – 55) | 0.008 |
| **Tested for HIV (n=181) | | | | |
| HIV positive | 69 (74.2) | 20 (100) | 45 (57) | 0.001+ |
| HIV negative | 19 (20.4) | 0 (00.0) | 28 (35.4) | |
| CD4+ count, n (%) | | | | |
| < 200 | 56 (60.2) | 12 (60.0) | 22 (27.9) | <0.001 |
| 200 ≤ 350 | 10 (10.7) | 3 (15.0) | 16 (20.3) | |
| > 350 | 27 (29.0) | 5 (25.0) | 41 (51.9) | |
| History of previous TB, n (%) | 13 (14.0) | 6 (30.0) | 15 (19.0) | 0.176† |
| Follow up in weeks, n (IQR) | 52 (21-102.6) | 60 (18.5-77.3) | 55 (10-81.3) | 0.561 |
| *Duration of symptoms before admission | | | | |
| † Fisher's exact test | | | | |
| §Only 124 out of 192 patients had a record of AF, of whom, 27 patients with definite TB pericarditis had presence / absence of AF recorded, 20 of those with probable disease and TB elsewhere and ^x only 77 patients with probable TB with no TB elsewhere had a record of presence/absence of AF | | | | |
| ** Only a 181 out of 192 patients were tested for HIV.(88 with definite TB had a record of an HIV test, 20 patients with probable and TB elsewhere and 73 with probable and no TB elsewhere had a record of an HIV test) | | | | |
| ¶only 184 out of the 192 patients had a record of presence or absence of tamponade, out of which, 87 patients with definite TB had a record of presence or absence of tamponade; 20 of those with probable TB with TB elsewhere had a record of presence or absence of tamponade and only 77 of the 79 patients admitted with probable disease and no TB elsewhere had a record of absence or presence of tamponade. | | | | |

Age in years; duration of symptoms in days; pulse in beats per minute; adenosine deaminase in IU/l; globulin in g/l; CD4+ in ; blood pressure in mmHg; showing number (n) and percentage of those with atrial fibrillation, HIV and previous TB and also showing the sex distribution by percentage in the groups explored. IQR -interquartile range

(Table 1) summarises the baseline characteristics of the study participants. A total of 192 patients were enrolled and then followed up for a median of 52.9 weeks (15.14 - 90.6). Of these, 93 (48.4%) were classified as having definite disease, 20 (10.4%) as having probable disease with TB proven elsewhere in the body and 79 (41.1%) as probable disease with no TB elsewhere in the body.

There was a difference in age distribution between the three groups with the median age in those with definite disease higher than the median age in the other two groups. The median age in those with definite disease was 34 years (30 - 45); 30 years (24.5 – 37) in those with probable disease with TB elsewhere and 30 years (26 – 41) in those with only probable disease; ($p = 0.020$).

There was no difference in the proportion of males and females enrolled when all three groups were compared. With males comprising 57 (61.3%) of those with definite disease, 10 (50%) of those with probable disease and TB elsewhere and 40 (50.6%) of those with probable disease only; ($p = 0.322$).

Based on clinical features, there was no difference in the duration of symptoms before admission between the three groups. The median duration of symptoms was 28 days (14 - 31) in the definite group, 24 days (14 - 38.5) in the probable with TB elsewhere group and 23 days (14 – 42) in the patients with probable but no proven TB elsewhere group; ($p = 0.692$).

When compared by blood pressure (BP) and pulse rates, there was no difference between the definite, probable with TB elsewhere and probable disease only groups. The median systolic pressure was 108 mmHg (97 -114) in the definite group; 100.5 mmHg (99 - 108) in the probable with TB elsewhere group and 105 mmHg (96 – 117) in those with probable but no TB elsewhere; ($p = 0.823$). Furthermore, the median diastolic pressure was 70 mmHg (64 – 80) in those with definite disease, 72.5 mmHg (61 – 80) in those with probable disease with

proven TB elsewhere and 70 mmHg (60 – 80) in those with probable disease but no TB elsewhere; ($p = 0.670$). The median pulse in all three groups was similar ($p = 0.180$). Those with definite disease had a median pulse of 114 bpm (101 – 126), those with probable disease and TB elsewhere 120 bpm (99 – 120) and in those with probable disease but no TB elsewhere 110 bpm (96 – 122). Additionally, the pulse pressure and mean arterial pressure were similar in the three groups; ($p = 0.586$ and $p = 0.657$, respectively).

Median ADA levels were lower in the patients with probable disease with no TB elsewhere 55 IU/l (30 – 81.9) than in those with probable disease but proven TB elsewhere, 75.3 IU/l (42.4 – 121) and those with definite disease, 73 IU/l (52.7 - 99); ($p = 0.025$). The latter two groups had similar ADA levels. The median globulin levels were highest in patients with definite disease, 54.5 gm/l (47.6 – 63), followed by those with probable disease with no TB elsewhere, 48 gm/l (43 – 55) and those with probable TB with TB elsewhere, 46.5 g/l (44 – 58); ($p = 0.008$).

The median duration of follow-up in all three groups was similar, ($p = 0.561$). Patients with definite disease had a median follow up of 52 weeks (21 – 102.6), those with evidence of TB elsewhere, 60 weeks (18.5 – 77.3) and those with probable disease but no TB elsewhere, 55 weeks (10 – 81.3).

Figure 2: Survival Analysis

Fig (2) presents the Kaplan-Meier survival curves of patients with definite disease, with probable disease with proven TB elsewhere and those with probable disease with no TB proven elsewhere.

Based on the analysis, the three groups do not differ in terms of survival; (Log rank: chi-squared test = 0.10, $p = 0.953$)

Using Cox regression analysis, we investigated the influence of selected demographic characteristics, clinical features and laboratory findings on mortality. The factors associated with mortality in the enrolled patients were examined using both a univariate and multivariate analysis. A step-wise model building was performed and the variables selected for regression analysis in the model were based on statistical significance.

A multivariate model was fitted based on step-wise model building.

(Table 2) below shows the results of the analyses performed.

Table 2. Cox proportional hazards regression analyses for time to death (N = 179)

| BASELINE CHARACTERISTIC | UNIVARIATE ANALYSIS | | | MULTIVARIATE ANALYSIS | | |
|----------------------------|---------------------|-------------|----------|-----------------------|------------|----------|
| | HR | 95% CI | <i>p</i> | HR | 95% CI | <i>p</i> |
| AGE | 1.03 | 1.01-1.05 | 0.015 | 1.02 | 0.998-1.04 | 0.082 |
| MALES | 0.796 | 0.395-1.60 | 0.522 | - | - | - |
| <i>Clinical features</i> | | | | | | |
| DURATION OF SYMPTOMS | 1.00 | 0.99-1.01 | 0.620 | - | - | - |
| SYSTOLIC BLOOD PRESSURE | 0.978 | 0.951-1.00 | 0.088 | - | - | - |
| DIASTOLIC BLOOD PRESSURE | 0.965 | 0.94-0.995 | 0.022 | 0.96 | 0.93-0.99 | 0.013 |
| PULSE PRESSURE | 1.01 | 0.98-1.04 | 0.524 | - | - | - |
| MEAN ARTERIAL PRESSURE | 0.95 | 0.92-0.98 | 0.04 | - | - | - |
| PULSE RATE | 1.01 | 0.99-1.02 | 0.483 | - | - | - |
| ATRIAL FIBRILLATION | 1.49 | 0.627-3.52 | 0.368 | - | - | - |
| TAMPONADE ON ADMISSION | 3.05 | 1.49-6.27 | 0.002 | 2.44 | 1.08-5.54 | 0.033 |
| <i>Laboratory findings</i> | | | | | | |
| CD4+ <200 | 0.73 | 0.308 –1.95 | 0.442 | - | - | - |
| CD4+ >200 | 0.49 | 0.133-1.77 | 0.272 | - | - | - |
| HIV | 1.20 | 0.677-2.14 | 0.527 | - | - | - |
| ADA | 0.99 | 0.99-1.01 | 0.392 | - | - | - |
| GLOBULIN (n=85) | 0.99 | 0.95-1.04 | 0.826 | - | - | - |
| TB ELSEWHERE | 1.24 | 0.49-3.15 | 0.654 | - | - | - |
| DIAGNOSTIC GROUP | 1.11 | 0.55-2.23 | 0.769 | - | - | - |

Predictors of mortality

From the univariate analysis, four variables which include age, diastolic BP, mean arterial pressure and the presence of tamponade on admission were significantly associated with mortality; a one year increase in age was associated with a 3% increase in the relative hazard of mortality ($p = 0.015$); a one mmHg rise in diastolic BP is associated with a 4% reduced hazard in mortality, ($p = 0.022$); a one mmHg rise in mean arterial pressure is associated with a 5% reduced relative hazard of mortality, ($p = 0.04$); and who were admitted in cardiac tamponade had a 3.05 times increased relative hazard of mortality when compared to those admitted without tamponade ($p = 0.002$).

The multivariate analysis obtained after adjusting for age, diastolic BP and tamponade on admission was interpreted as follows:

A one year increase in age is associated with 2% increased relative hazard of mortality (95% CI: 0.998 - 1.04). The results are not statistically significant at $p = 0.082$.

Similarly every mmHg rise in diastolic pressure is associated with a 4% reduced relative hazard of mortality (95% CI: 0.932 - 0.998). The results are statistically significant at $p = 0.013$.

Those with cardiac tamponade on admission had a 2.44 times increased relative hazard of mortality when compared to those admitted without tamponade. (95% CI: 1.08 - 5.54). The results are statistically significant at $p = 0.033$.

Complications of TB pericarditis

Over a 6 year follow-up period, 11 (5.7%) of the 192 patients needed recurrent pericardial aspirations. The overall incidence rate for recurrent pericardial effusions was 47.1 cases per 1000 person years. In those with definite disease the incidence rate was 32.9 cases per 1000 person years (12.3 - 87.7); in those with probable TB pericarditis with TB elsewhere the incidence rate was 92.1 cases per 1000 person years (23.04 - 368.4) and in those with probable TB pericarditis without TB elsewhere, incidence was 55.5 cases per 1000 person years (23.1 - 133.3). Using Definite TB pericarditis as a reference group, when compared to probable pericarditis with TB elsewhere and probable pericarditis with no TB elsewhere $p < 0.001$ and 0.007 , respectively. Incidence was lowest in the group with definite TB pericarditis.

During a follow-up period of 6 years, 30 (15.63%) patients developed constrictive pericarditis. The overall incidence rate was 132.2 cases per 1000 person-years (92.45 - 189.12). In those with definite disease the incidence was 146.6 cases per 1000 person-years (91.13 - 235.82); in those with probable TB pericarditis with TB elsewhere the incidence rate was 138.5 cases per 1000 person-years (44.7 - 429.44) and in those with probable TB pericarditis without TB elsewhere, incidence was 112.04 cases per 1000 person years (60.3 - 208.2). Using Definite TB pericarditis as a reference group, when compared to probable pericarditis with TB elsewhere and probable pericarditis with no TB elsewhere $p = 0.318$ and $p = 0.057$, respectively. There was no significant difference in incidence of constrictive pericarditis between the 3 groups.

The overall incidence rate of those needing pericardiectomy was 34.4 cases per 1000 person-years (17.2 - 68.8). In those with definite disease the incidence rate was 32.9 cases per 1000 person-years (12.3 - 87.7); in those with probable TB pericarditis with TB elsewhere the

incidence rate was 46.2 cases per 1000 person-years (6.5 - 327.7) and in those with probable TB pericarditis without TB elsewhere, incidence was 33.6 cases per 1000 person years (10.8 - 104.2). Using Definite TB pericarditis as a reference group, when compared to probable pericarditis with TB elsewhere and probable pericarditis with no TB elsewhere $p=0.07$ and 0.45 , respectively There was no significant difference in incidence of pericardiectomy between the 3 groups.

Discussion

TB pericarditis is a treatable condition that still causes severe morbidity and mortality. ⁽¹⁾

In our study *M tuberculosis* was identified in the pericardial fluid or tissue of 93 (48.4%) of the patients thus assigning them as definite TB pericarditis whilst the remaining 99 (51.6%) were classified as probable disease of which 79 (41.1%) were classified as probable disease with no proof of TB elsewhere (except the heart) and 20 (10.4%) as probable disease with proof of TB elsewhere.

The patient population had an overall mortality of 36 (18.8%) over the 6 year follow-up period. This rate is better than other studies conducted in TB pericarditis in which mortality ranged from 17 to 40%. ⁽⁵⁾ An earlier prospective study on mortality in patients treated for TB pericarditis had an overall mortality rate of 26% with mortality as high as 40% in those with clinical HIV disease over a 6 month period. ⁽¹⁾. An important difference between that study and the current one is that only 14.1% of their patients underwent pericardiocentesis, unlike the current study in which all patients underwent the procedure. This suggests that pericardiocentesis may have a beneficial role in managing patients in addition to anti-TB treatment. ⁽¹⁾

There was no difference in mortality between those with definite disease, probable disease with TB elsewhere or those with probable disease with no TB elsewhere (20.4%, 20.0% and 16.5% respectively; $p = 0.799$). It is known that extrapulmonary specimens yield lower bacillary loads and are consequently associated with low sensitivities in smear and culture. ⁽⁶⁾ It is hypothesized that bacillary density, whilst not routinely quantified, is higher in those with definite as opposed to probable disease, and thus more likely to be associated with a higher mortality in the former when both are subjected to similar treatment regimens. ^(6,7) Our study does raise the question as to the clinical utility of the distinctions between probable and definite entities as it relates to outcomes in patients with TB pericarditis.

Our results were in stark contrast to a study carried out in patients with tuberculous meningitis, a condition that also poses diagnostic and therapeutic difficulty, in which mortality was higher in patients with proven meningeal tuberculosis as compared to patients with probable disease (78% and 38% respectively p -value <0.0001)⁽⁷⁾. The results also differed from a study performed in India, in which the 18 month mortality was highest in those with smear positive disease (34.7%) and lowest in those with smear and culture negative disease (5%). ⁽⁸⁾ The aforementioned studies gave credence to our original hypothesis, but our findings suggest that this is not the case in TB pericarditis.

The main factors that predicted mortality in this population were the presence of cardiac tamponade on admission, age and a low diastolic blood pressure prior to pericardiocentesis.

It could be seen that increasing age was associated with a higher mortality, as confirmed by other studies.⁽¹⁾ It would have been important to determine the co-morbidities and causes of death in this group of patients as it is likely that poorer states of physical health in older patients is responsible for this finding .

A low diastolic pressure may be part of the physical findings in tamponade, although it may exist independently of it. Regardless of whether patients had definite or probable disease, a low diastolic blood pressure was a predictor of mortality. This occurred independently of systolic blood pressure. The mean arterial pressure was an independent predictor of mortality but on adjustment, failed to improve the predictive model.

ADA was also confirmed as a tool for use in making an indirect diagnosis of TB pericarditis.^(9,10) Although ADA was not important as a predictor for death ($p = 0.392$), it was significant as a marker for distinguishing between definite, probable disease with TB elsewhere and probable disease with no TB elsewhere, (p-value 0.025).

Constrictive pericarditis is known to occur in almost all patients with untreated TB pericarditis and in 30% to 50% of those who receive anti-TB treatment within the first 6 months of therapy.^(11,12) Constriction developed in 15% of the patients with an overall incidence rate of 132.2 cases per 1000 person–years. The rate is significantly lower than that reported by Imazio et al of 31.65 cases per 1000 person-years of the 20 enrolled TB pericarditis patients who developed constriction.⁽¹³⁾ Consequent to severe constriction, pericardiectomy may be performed. In a study by Sagrista –Sauleda et al, 57% of their patients developed constriction and all proceeded to undergo pericardiectomy.⁽¹⁴⁾ The overall incidence rate of pericardiectomy in our study was lower at 34.4 cases per 1000 person – years. The incidence rate of recurrent pericardial effusions needing aspiration was 47.1 cases per 1000 person-years rate. The incidence of all complications was lower than expected. It must be noted that the status of constriction was determined based on file records, and if the diagnosis was made at a different centre, there was no way of retrieving this information.

In conclusion, survival in patients with TB pericarditis is not influenced by whether the disease is definite or probable. This information is important in resource-limited areas where diagnostic facilities are limited. Mortality, however, remains unacceptably high in both groups of patients. Prospective studies are needed to determine causes of death despite availability of treatment.

Limitations

The main limitation of this study was that being a retrospective study, not all results were available. The complications that occurred in patients that were referred back to other facilities was difficult to ascertain in the majority of patients.

Finally, Misclassification of patients with TB elsewhere as only TB pericarditis may have occurred if TB elsewhere not looked for or recorded by the examining physician as most patients were referred for pericardial aspiration.

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APPENDIX A: 1. Showing excluded participants

Table 3. 'Baseline characteristics of the study participants who were excluded'

| RISK FACTOR | Definite TB pericarditis n=62 | Probable with TB elsewhere n= 16 | Probable with no TB elsewhere n= 79 | <i>p-value</i> |
|--|--|---|--|----------------|
| Age (years), median (IQR) | 35 (29-44) | 32.5 (27-37.5) | 37 (30-46) | 0.305 |
| Sex: Male, n (%) | 39 (47.6) | 6 (7.3) | 37 (45) | 0.076 |
| <i>Clinical Features</i> | | | | |
| Duration* (days), median (IQR) | 31 (28-34) | 24 (14-90) | 14 (7-22) | 0.172 |
| Pulse (bpm), median (IQR) | 102(97-113) | 114 (98-130) | 100 (98-111) | 0.904 |
| Systolic BP, median (IQR) | 95 (89-105) | 106 (100-112) | 108 (100-120) | 0.204 |
| Diastolic BP, median (IQR) | 64 (56.5-69) | 64 (60-68) | 70 (60-72) | 0.352 |
| Pulse pressure, median (IQR) | 33.5 (31-37.5) | 42 (40-44) | 41.5 (30-50) | 0.418 |
| Mean arterial pressure, median (IQR) | 74.4 (67.4-81) | 78 (73.3-82.7) | 80.9(75– 86.7) | 0.341 |
| Atrial Fibrillation, n (%) | 4 (17.4) | 2 (11.1) | 17 (17.7) | 0.230+ |
| Tamponade, n (%) | 3 (75) | 1 (50) | 7 (43.8) | 0.380+ |
| <i>Laboratory features</i> | | | | |
| ADA (IU/L) median (IQR) | 65 (46-88) | 47 (34.3-74) | 47.3 (25-60.9) | 0.052 |
| Globulin (gm/l), median (IQR) | 47.5 (43.5-58) | 48 (39-56) | 47 (40 – 53) | 0.94 |
| Tested for HIV | | | | |
| HIV positive | 28 (22.2) | 11 (91.7) | 30 (37.7) | 0.033+ |
| HIV negative | 6 (40.6) | 1 (8.33) | 20 (56.6) | |
| CD4+ count, n (%) | | | | |
| < 200 | 20 (32.3) | 7 (43.8) | 18 (22.8) | 0.04 |
| 200 ≤ 350 | 7 (11.3) | 5 (31.25) | 11 (13.9) | |
| > 350 | 35 (56.5) | 4 (25.0) | 50 (63.3) | |
| Follow up in weeks, n (IQR) | 14.4 (1-27.9) | 99.6 (n=1) | 14 (4.4-81) | 0.296 |
| *Duration of symptoms before admission | | | | |
| † Fisher's exact test | | | | |

Age in years; duration of symptoms in days; pulse in beats per minute; adenosine deaminase in IU/l ; globulin in g/l; CD4+ in ; blood pressure in mmHg ; showing number (n) and percentage of those with atrial fibrillation, HIV and previous TB and also showing the sex distribution by percentage in the groups explored. IQR -interquartile range

(Table 3) summarises the baseline characteristics of the excluded participants. A total of 157 patients were excluded. Of these, 39.5% were classified as having definite disease, 10.2% as

having probable disease with TB proven elsewhere in the body and 50.3% as probable disease with no TB elsewhere in the body.

When the included and excluded participants were compared by using the p-values of the baseline characteristics comparing, the only differences noted were that there was no difference in globulin levels in the excluded group, while the levels were different in the included group. There was also no difference in age in the excluded participants whilst the included ones showed a difference in age between the three groups based on p-values to determine the level of statistical significance. All the other variables were comparable.

Table 4: Showing number of missing variables

| VARIABLE | MISSING DATA n (%) | TOTAL AVAILABLE n (%) |
|-----------------------------|---------------------------|------------------------------|
| AGE | - | 214 (100%) |
| SEX | - | 214 (100%) |
| DURATION OF SYMPTOMS | - | 214 (100%) |
| PREVIOUS TB | 27 (12.6%) | 187 (87.4%) |
| SYSTOLIC BP | 04 (1.9%) | 210 (98.1%) |
| DIASTOLIC BP | 04 (1.9%) | 210 (98.1%) |
| PULSE RATE | 04 (1.9%) | 210 (98.1%) |
| ATRIAL FIBRILLATION | 09 (4.2%) | 205 (95.8) |
| TAMPONADE | 10 (4.7%) | 204 (95.3%) |
| ADA | 29 (13.6%) | 185 (86.4%) |
| GLOBULIN | 118 (55%) | 96 (45%) |
| HIV STATUS | 13 (6.1%) | 201 (93.9%) |
| TB ELSEWHERE | 51 (23.8%) | 163 (76.2%) |

The table above describes characteristics in 214 patients who had fairly complete data. The greatest determinant for selecting the included patients from the above cohort was the presence of a diagnosis for TB elsewhere as this helped determine the groups of analysis.

There was no missing data for baseline age, gender and duration of symptoms prior to admission in 214 patients. In 27 (12.6%) patients, there was no recorded history of tuberculosis, and in 51 there was no documentation of TB in another part of the body.

In 4 (1.96%) patients, there was no recorded blood pressure or pulse prior to pericardiocentesis. Furthermore, pulse was not characterized in 9 (4.2%) and thus no record

of the presence or absence of atrial fibrillation. In 10 (4.7%) patients, there was no record of tamponade or insufficient information to classify them as having tamponade or not.

There was no information on ADA for 29 (13.6%) patients. This was due either to insufficient specimen samples and/or hemolysis in collected pericardial specimens. Similarly for globulin, there was missing data nearly half the patients (55%); this was due to the investigation not being routinely requested for patients who were being referred to the GSH purely for pericardiocentesis.

Of the missing HIV data, in 7 out of the 13 patients who status was not known, refusal to grant consent was recorded as the reason for not having a test result, whilst in the remainder no mention was found of status.

The preliminary data exploration which looked at Wilcoxon sum rank tests, chi-squared and Fischer's tests used the available data as is. For the Cox Proportional Hazards regression, data on 179 patients was used as this was complete for the examined variables.

APPENDIX B

QUESTIONNAIRE

THE INVESTIGATION OF MANAGEMENT OF PERICARDITIS (IMPI)
SURVIVAL OUTCOMES SUB-STUDY

INTERVIEW: _ _ _ _

IDENTIFICATION NUMBER: _ _ _ _

HOSPITAL FOLDER NUMBER _____

FOLLOW-UP CLINIC _____

DATE OF PERICARDIOCENTESIS __ / __ / _ _ _ _

IDENTIFICATION

NAME: _____
(Last) (First) (MI)

STREET _____

AREA _____ POSTCODE _____

PHONE NUMBER: () _____ - _____

DATE: _____

ID NUMBER _____

DATE OF BIRTH __ / __ / __

SEX M F

AGE AT ENROLLMENT __ YEARS

Nationality:

RSA OTHER SPECIFY.....

DIAGNOSIS

DURATION OF SYMPTOMS ___ ___ DAYS

DIAGNOSIS OF PERICARDITIS

PROBABLE OR DEFINITE

IF PROBABLE

- POSITIVE SPUTUM M/C/S
- POSITIVE LYMPHNODE/ PLEURAL/ URINE M/C/S
- ADA LEVEL ___
- HIGH LYMPHOCYTES IN PERICARDIAL FLUID

IF DEFINITE

- POSITIVE PERICARDIAL Microscopy
- POSITIVE CULTURE
---- DAYS TO POSITIVE CULTURE
- POSITIVE PCR
- POSITIVE PERICARDIAL HISTOLOGY

HEMODYNAMIC STABILITY ON ADMISSION:

- SYSTOLIC BP < 100 mmHg ___ mmHg
- PULSE RATE > 100 bpm ___ bpm
- ATRIAL FIBRILLATION
- RIGHT ATRIAL & VENTRICULAR COLLAPSE
- STABLE

CO-MORBID CONDITIONS

HIV STATUS

POSITIVE NEGATIVE UNKNOWN

BASELINE CD4 COUNT _ _ _ _

IF POSITIVE:

- USE OF ART PRIOR TO TB DIAGNOSIS > 6 MONTHS
- USE OF ART PRIOR TO TB DIAGNOSIS < 6 MONTHS
- COMMENCED ART WITHIN 3 MONTHS OF STARTING TB TREATMENT
- COMMENCED ART TREATMENT > 3 MONTHS OF STARTING TB TREATMENT
- DID NOT START TB TREATMENT

ORAL STEROID USE

YES NO NOT RECORDED.

OTHER ILLNESSES

- PREVIOUS TB
- UNDERLYING CARDIOVASCULAR DISEASE
- DIABETES MELLITUS
- ASTHMA
- OTHER DISEASE SPECIFY _____

ALCOHOL – YES - NO

SMOKER YES NO

OCCUPATION _____

OUTCOME

DURATION OF FOLLOW UP IN MONTHS ___ __

DATE OF LAST FOLLOW-UP VISIT __ / __ / __

- LOST TO FOLLOW UP
- CONSTRICTION
- RECURRENT PERICARDIOCENTESIS
- PERICARDIECTOMY
- DIED

OUTCOME SOURCE

- HOSPITAL FOLDER
- DAY CLINIC RECORDS
- PATIENT
- NEXT OF KIN
- Clinicom database
- HOME AFFAIRS DATA BASE

APPENDIX C – MANUSCRIPT GUIDELINES

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Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

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References to ethnic classification must indicate the rationale for this.

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Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e. 'women >40 years of age'. The same applies to \pm and $^{\circ}$, i.e. '35 \pm 6' and '19 $^{\circ}$ C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

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Internet references:

World Health Organization. *The World Health Report 2002 - Reducing Risks, Promoting Healthy Life*. Geneva: World Health Organization, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

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