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DISSERTATION PROPOSAL

Efficacy and Safety of Intrapleural Fibrinolytic Therapy in Tuberculous Pleural Effusion Versus Non-Tuberculous Pleural Infection: A Ten-Year Retrospective Study at Hospital Canselor Tuanku Muhriz (**FIB-TB Study**)

CANDIDATE:

DR VINOD RAJ A/L MANIKAM (P 126597)

MAIN SUPERVISOR:

DR MAS FAZLIN BINTI MOHAMAD JAILAINI

Respiratory Unit, Internal Medicine Department, Hospital Canselor Tuanku Muhriz

CO SUPERVISOR:

PROFESSOR DR MOHAMED FAISAL ABDUL HAMID

Respiratory Unit, Internal Medicine Department, Hospital Canselor Tuanku Muhriz

DR AZAT AZRAI DATO' AZMEL

Respiratory Unit, Internal Medicine Department, Hospital Canselor Tuanku Muhriz

RADIOLOGY:

DR. ISA AZZAKI BIN ZAINAL

DR NIK FARHAN NIK FUAD

STATISTICIAN ADVISOR:

PROFESSOR DR SHAMSUL AZHAR SHAH

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LIST OF ABBREVIATION

1. EXTRAPULMONARY TUBERCULOSIS (EPTB)
2. TUBERCULOUS PLEURAL EFFUSION (TPE)
3. TUBERCULOUS PLEURISY (TP)
4. TUBERCULOSIS (TB)
5. ANTI-TUBERCULOUS THERAPY (ATT)
6. INTRAPLEURAL FIBRINOLYTIC THERAPY (IPFT)
7. RECOMBINANT DEOXYRIBONUCLEASE (DNASE)
8. PLASMINOGEN ACTIVATOR (TPA)

CHAPTER 1

INTRODUCTION

Globally, tuberculosis (TB) remains a major public health problem and a leading cause of infectious disease-related morbidity and mortality. Pleural tuberculosis is one of the most common forms of extrapulmonary TB, particularly in high-burden countries such as Malaysia.[2] Tuberculous pleural effusion (TPE) commonly presents with fever, pleuritic chest pain, cough, and dyspnoea, but these manifestations overlap with other causes of exudative pleural effusion, making diagnosis challenging.

In some patients, pleural inflammation leads to fibrin deposition, septation formation, and loculated effusions, resulting in impaired pleural fluid drainage.[11] Complicated or loculated TPE may cause persistent symptoms, prolonged hospitalization, incomplete lung re-expansion, residual pleural thickening, and occasionally fibrothorax.[1] Standard management includes anti-tuberculous therapy, therapeutic thoracentesis or chest tube drainage, and supportive care.

Despite appropriate anti-tuberculosis therapy, approximately 25% of patients with TPE develop residual pleural thickening at the completion of treatment. This is particularly common in patients with loculated pleural effusions, where fibrin septations impede effective pleural fluid drainage, resulting in persistent pleural inflammation and fibrosis. Furthermore, loculated TPE is often difficult to drain adequately using chest tube drainage alone, as the fibrinous septations compartmentalize the pleural fluid into multiple locules. Intrapleural fibrinolytic therapy (IPFT) may overcome this limitation by lysing fibrin septations, thereby improving pleural fluid drainage, facilitating lung re-expansion, and potentially reducing the incidence and severity of residual pleural thickening.

Intrapleural fibrinolytic therapy, particularly using tissue plasminogen activator (tPA) with or without DNase, has been increasingly used to improve pleural drainage by lysing fibrin septations. Its efficacy in non-tuberculous pleural infection and empyema is well established. Randomized controlled trials, including the MIST-2 study, demonstrated that combined tPA

and DNase therapy improves radiological clearance, reduces surgical referral, and shortens hospital stay, whereas tPA or DNase alone provides limited benefit.[15]

Although, combined intrapleural tPA and DNase therapy is increasingly used, its mechanisms of action within the infected pleural cavity remain incompletely understood. Current treatment protocols are largely based on empirical practice, as the optimal dosage, administration frequency, sequence, and method of drug instillation have yet to be established.[15]

However, the evidence supporting IPFT in TPE remains limited. Unlike non-tuberculous pleural infection, TPE is primarily driven by a delayed hypersensitivity response to Mycobacterium tuberculosis antigens rather than direct purulent bacterial infection, and therefore treatment outcomes may differ. Therefore, a significant knowledge gap remains regarding the efficacy and safety of IPFT in TPE compared with non-tuberculous pleural infection.

Moreover, there were no randomized controlled trials have specifically evaluated IPFT in patients with TPE, and the available evidence is limited to small case series and observational studies, including local data from Universiti Kebangsaan Malaysia (UKM) demonstrating potential benefits of intrapleural alteplase, with or without DNase, in improving pleural drainage and clinical outcomes without significant bleeding complications. However, these studies are limited by small sample sizes, the absence of control groups, and potential selection bias, thereby precluding definitive conclusions.

Therefore, this study aims to address these gaps by evaluating the clinical characteristics, efficacy, safety and outcomes of patients with particular emphasis on the role of IPFT in complicated TPE cases over a ten-year period at Hospital Canselor Tuanku Muhriz (HCTM).

CHAPTER 2

LITERATURE REVIEW

Tuberculosis remains a major global public health challenge. According to the WHO Global Tuberculosis Report 2025, an estimated 10.7 million people developed TB in 2024, corresponding to an incidence of approximately 131 cases per 100,000 population worldwide.[2] Extrapulmonary tuberculosis accounts for approximately 15–20% of TB cases in immunocompetent individuals and up to 50% among people living with HIV, with TPE being one of its most common manifestations.[9,10] Moreover, the prevalence of multidrug-resistant TB is higher in patients with EPTB than in pulmonary TB, with pleural TB showing an increase from 17.3% to 35.7% MDR cases over recent years.[2,8]

Moreover, TPE presents unique diagnostic challenges due to its paucibacillary nature, meaning that the bacterial load in pleural fluid is low, resulting in poor microbiological diagnostic yield. [2,7] The pathogenesis of TPE arises from rupture of a subpleural caseous focus releasing mycobacterial antigens into the pleural space, triggering a delayed-type hypersensitivity reaction, rather than direct bacterial invasion.[2,3] This results in a lymphocyte-predominant exudative pleural effusion characterized by elevated protein levels and inflammatory markers. This Th1-mediated immune response results in lymphocytic infiltration, granuloma formation, and impaired lymphatic drainage. While most effusions are lymphocyte predominant, approximately 10% demonstrate neutrophilic predominance, correlating with higher mycobacterial burden and increased loculation.[7]

Compared with other causes of pleural effusion, patients with TPE are generally younger and have fewer chronic comorbidities, whereas non-tuberculous effusions such as malignant or parapneumonic effusions are more commonly observed in older individuals with multiple underlying medical conditions. Clinically, TPE typically presents as an acute or subacute illness with pleuritic chest pain, cough, fever, and dyspnoea. Most effusions are unilateral and occupy less than two-thirds of the hemithorax.[10] Coexistent pulmonary disease

is detected on chest radiography in 18–50% of cases and on computed tomography in up to 85%. Radiological features such as loculation and pleural thickening may persist as fibrothorax even after microbiological cure.[7]

Tuberculous pleural infection remains diagnostically challenging because of the low diagnostic yield of conventional pleural fluid investigations. Pleural fluid analysis typically demonstrates a straw-coloured, lymphocyte-predominant exudate with elevated protein and lactate dehydrogenase (LDH) levels.[2] Approximately 75% of patients with TPE have pleural fluid LDH levels exceeding 500 IU/L.[11] However, LDH alone lacks sufficient specificity to distinguish TPE from other inflammatory exudative pleural effusions, particularly parapneumonic effusion and empyema. Additionally, measurement of adenosine deaminase (ADA) levels in pleural fluid provides a reliable adjunctive tool, with reported sensitivity and specificity of approximately 92% and 90%, respectively.[13] In contrast, the combination of a pleural fluid lymphocyte-to-neutrophil ratio >0.75 and elevated ADA has a reported sensitivity of 88% and specificity of 95% for diagnosing TPE.[7]

In many TB-endemic regions, an ADA cutoff value of 40 U/L is widely used to support the diagnosis of TPE in patients with lymphocyte-predominant exudative pleural effusion. However, the optimal diagnostic threshold may vary according to local epidemiology. In Malaysia, a multicentre study demonstrated that a lower ADA cutoff of 36 U/L improved diagnostic sensitivity while maintaining acceptable specificity, consistent with findings from other Asian populations, including Hong Kong.[11]

Pleural fluid culture positivity ranges from 7–63%, while acid-fast bacilli staining is positive in fewer than 10% of cases.[7,10] *Mycobacterium tuberculosis* cultures from pleural fluid show variable sensitivity ranging from 24% to 58%. In contrast, pleural biopsy obtained via closed needle techniques or medical thoracoscopy, continues to serve as the diagnostic gold standard, offering sensitivities of up to 93%. However, thoracoscopy is not widely available in many high-TB-burden settings and may not be feasible due to cost and resource limitations.[11]

In contrast, PCR-based tests such as Xpert MTB/RIF and Xpert Ultra allow rapid detection and limited rifampicin resistance profiling, though sensitivity remains variable.[10] Therefore, establishing a definitive diagnosis of tuberculous pleural effusion remains clinically challenging. Given these diagnostic limitations, many clinical studies adopt a composite

reference standard for the classification of tuberculous pleural effusion. Patients are commonly categorized into definite TPE, clinical TPE, and non-tuberculous pleural effusion. Definite TPE refers to cases with microbiological or histopathological confirmation of *Mycobacterium tuberculosis*, including positive pleural fluid culture, acid-fast bacilli staining, positive molecular testing, or demonstration of caseating granuloma on pleural biopsy.

Clinical TPE refers to patients who lack microbiological confirmation but demonstrate clinical, radiological, and epidemiological features suggestive of tuberculosis, often accompanied by a favourable response to anti-tuberculosis therapy. Non-tuberculous pleural effusion includes patients with alternative diagnoses or absence of evidence supporting tuberculosis infection. This classification approach reflects the real-world diagnostic challenges encountered in TB-endemic regions where microbiological confirmation may not always be achievable.[11]

The primary management of tuberculous pleural effusion involves prompt initiation of anti-tuberculosis therapy, which usually leads to gradual resolution of the pleural effusion and improvement in clinical symptoms. Moreover, both the World Health Organization (WHO) and the American Thoracic Society (ATS) recommend a six-month anti-tuberculosis treatment regimen for pleural tuberculosis, which is consistent with the standard therapeutic approach used for pulmonary tuberculosis.[13] However, some patients may develop complications such as persistent pleural fluid accumulation, loculated effusions, pleural thickening, or incomplete lung re-expansion. In such cases, additional interventions such as therapeutic thoracentesis or pleural drainage may be required to facilitate lung expansion and relieve symptoms.[1,11] Corticosteroids are generally not recommended.

Symptomatic tuberculous pleural effusions generally benefit from pleural drainage, although the role of therapeutic thoracentesis as an adjunct to anti-tuberculosis therapy remains controversial. Standard anti-TB therapy alone may be insufficient, and up to one-third of patients experience inadequate pleural drainage. Therefore, therapeutic drainage may be considered in selected patients, particularly those with large or symptomatic effusions. Surgical intervention, including decortication or pleurectomy, is reserved for chronic or complicated cases with persistent sepsis or inadequately drained loculated effusions, although postoperative morbidity may be as high as 33%.[7] Hence, surgical decortication is reserved for cases with ongoing sepsis and inadequately drained complex effusions, with the decision guided by the patient's overall clinical fitness.

Moreover, the optimal timing of surgical intervention in tuberculous empyema continues to be debated among pulmonologists and thoracic surgeons. In general, surgery is performed after at least two months of anti-tuberculosis therapy to allow sufficient reduction in mycobacterial burden prior to intervention. However, excessive delay in surgical management may result in clinical deterioration and is associated with increased perioperative mortality.[13] Surgical interventions such as thoracotomy or VATS are effective but invasive and costly.[5]

Intrapleural fibrinolytic therapy was first introduced in the late 1940s using a crude preparation containing streptokinase and streptococcal DNase. Early studies demonstrated enhanced fibrin degradation, reduced pus viscosity, and improved pleural drainage. During the 1980s and 1990s, streptokinase and urokinase were further evaluated in several small studies, which reported improved pleural drainage and reduced surgical intervention. However, these studies were limited by small sample sizes and inconsistent findings.[15]

The Multicenter Intrapleural Sepsis Trial (MIST-1) was the first large randomized controlled trial evaluating intrapleural streptokinase (250,000 IU twice daily for three days). The trial demonstrated no significant improvement in mortality, need for surgery, radiographic resolution, or length of hospital stay compared with placebo. Furthermore, streptokinase was associated with a higher incidence of adverse events, including chest pain, fever, and allergic reactions, thereby questioning the routine use of fibrinolytic monotherapy in pleural infection.[15]

Subsequent studies demonstrated that fibrinolytic agents and DNase have complementary mechanisms of action. Tissue plasminogen activator (tPA) lyses fibrin septations within loculated pleural collections, whereas DNase degrades extracellular DNA released from inflammatory cells, reducing pus viscosity and facilitating pleural drainage. In particular, animal studies confirmed that combined tPA and DNase produced greater pleural fluid drainage and superior empyema resolution than either agent alone, providing the rationale for subsequent clinical trials.[15]

In contrast, the Multicenter Intrapleural Sepsis Trial-2 (MIST-2) was a multicentre, randomized, double-blind, placebo-controlled trial involving 196 patients with pleural infection. Participants were randomized to receive tPA alone, DNase alone, combined tPA/DNase, or placebo. The combination of tPA and DNase significantly improved radiographic clearance of pleural collections, reduced referral for surgery, and shortened hospital stay by approximately 6.7 days compared with placebo. Approximately 96% of

patients receiving combination therapy were successfully managed without surgery, although no significant mortality benefit was observed. In contrast, neither tPA nor DNase monotherapy demonstrated significant clinical benefit, with DNase alone showing a higher rate of surgical referral than placebo.[15]

Patients with tuberculous pleural effusion were represented only in the placebo arm of the MIST-2 trial, thereby limiting the applicability of these findings to tuberculosis-related pleural disease.[3,12,15] Based on the MIST-2 protocol, intrapleural alteplase (10 mg) and DNase (5 mg) are administered twice daily for three days, giving a maximum of six doses. This regimen has become the standard adjunctive treatment for complicated parapneumonic effusion and empyema. However, the protocol was developed empirically, and the optimal dosage, dosing interval, sequence of administration, and whether both agents can be administered simultaneously remain uncertain. In contrast, at Hospital Canselor Tuanku Muhriz, intrapleural alteplase is routinely administered at a dose of 16 mg combined with DNase 5 mg for three doses, based on local formulary constraints that optimize utilisation of the 50-mg alteplase vial within its recommended period after reconstitution.[13]

Combined tPA/DNase therapy has demonstrated an acceptable safety profile. The most common adverse event is chest pain, particularly following the first dose, occasionally requiring opioid analgesia. Pleural bleeding is uncommon but remains the principal safety concern. In MIST-2, two cases of intrapleural haemorrhage and one episode of haemoptysis occurred among 48 patients receiving combination therapy, although the overall rate of serious adverse events was not significantly different from placebo. Subsequent observational studies have similarly reported a low incidence of major bleeding (approximately 1–2%), predominantly in patients with underlying bleeding risk factors such as anticoagulant therapy or end-stage renal disease.[15] In addition, older age and delayed initiation of IPFT were predictors of poorer outcomes in MIST-2 study.[5]

Despite these favourable outcomes in non-tuberculous pleural infection, evidence supporting IPFT in tuberculous pleural effusion remains limited. No randomized controlled trial has specifically evaluated IPFT in TPE, and the available literature consists primarily of small retrospective studies and case series.

The evidence gap is further compounded by the distinct pathophysiology of tuberculous pleural effusion, which is primarily mediated by a delayed hypersensitivity reaction rather than

direct purulent bacterial infection. Consequently, it remains uncertain whether the established benefits of IPFT in non-tuberculous pleural infection can be extrapolated to TPE. Further comparative studies are therefore required to evaluate the efficacy and safety of IPFT in tuberculous pleural effusion and to establish evidence-based treatment recommendations.

A retrospective analysis at Tan Tock Seng Hospital involving 131 patients with non-TPE reported treatment success of 85.5%, defined as survival without surgery at three months. Radiological improvement was comparable across dose groups, supporting individualized lower-dose strategies.[6] Local Malaysian data comparing IPFT and surgery showed that patients undergoing IPFT had a mean age of 55.2 ± 18.6 years versus 44 ± 15.1 years in the surgical group ($p = 0.029$). IPFT was associated with significantly fewer immediate complications (27.5% vs. 94%; $p < 0.0005$). Early radiographic improvement was similar between groups, and adverse effects were generally mild.[6]

Understanding the clinical outcomes and safety profile of IPFT in TPE compared with non-tuberculous pleural infection may provide valuable insights into optimizing management strategies in TB-endemic settings. In summary, IPFT has become an evidence-based treatment for complicated parapneumonic effusion and empyema, its role in tuberculous pleural effusion remains uncertain because no randomized controlled trial has specifically evaluated this population. Current evidence consists primarily of retrospective studies and case series with limited sample sizes and heterogeneous treatment protocols. Furthermore, no comparative study has evaluated the efficacy and safety of IPFT between tuberculous and non-tuberculous pleural infection at HCTM.

Therefore, this study aims to evaluate the characteristic of TPE patient, efficacy and safety of IPFT in patients with tuberculous pleural effusion and compare the outcomes with those observed in patients with non-tuberculous pleural infections at HCTM. In addition, the outcomes of this study are expected to provide evidence-based support for current practices at HCTM, ensuring that intrapleural fibrinolysis, as an adjunct to standard care in complex tuberculous pleural effusion cases, is guided by documented efficacy and patient outcomes. If demonstrated to be effective, the results could inform local clinical protocols, optimize patient management, and potentially reduce hospital stay and complications related to persistent pleural effusions.

CHAPTER 3

RESEARCH OBJECTIVES

3.1 Objectives

3.1.1 Primary

To compare the efficacy of IPFT between TPE and non-TPE patients at HCTM over a ten-year period using percentage pleural opacity reduction on chest radiographs measured from Day 0 (prior to IPFT initiation) to Day 7–10 after IPFT initiation or the earliest available follow-up radiograph, whichever occurred earlier, using Horos software version 3.3.2 for radiological measurement.

3.1.2 Secondary

1. To describe the demographic and clinical characteristics of patients diagnosed with tuberculous pleural effusion at Hospital Canselor Tuanku Muhriz.
2. To compare the clinical outcomes of patients receiving IPFT between tuberculous pleural effusion and non-tuberculous pleural effusion, including:
    a. Clinical improvement of symptoms (e.g., fever, shortness of breath, cough, and pleuritic chest pain), as recorded in the patients' medical records from Day 0 (before initiation of IPFT) to Day 7–10 after initiation of IPFT or before hospital discharge, whichever occurs earlier.
    b. Volume of pleural fluid drainage (mL) following IPFT administration, drained via the pleural catheter during the first 24 hours after the initial IPFT dose and the total cumulative volume from initiation of IPFT until chest tube removal.
    c. Reduction in inflammatory markers (C-reactive protein, CRP) and total white cell count ($\times 10^9$/L) from baseline Day 0 (before initiation of

IPFT) to Day 7–10 (after initiation of IPFT, or the last available measurement before hospital discharge, whichever occurs earlier.)

d. Requirement for surgical intervention (e.g., decortication or video-assisted thoracoscopic surgery) within 30 days following initiation of IPFT due to failure of medical management.

3. To identify predictors of treatment-related adverse events in patients with tuberculous pleural effusion.

a. Chest pain requiring analgesic treatment.

b. Pleural bleeding or haemothorax.

c. Secondary pleural infection or empyema attributable to IPFT.

3.1.2 Research Question

What is the efficacy, safety, and clinical outcomes of IPFT in patients with tuberculous pleural effusion compared with patients with non-tuberculous pleural infections treated with IPFT at Hospital Canselor Tuanku Muhriz over a ten-year period?

3.1.4 Hypothesis

1. The efficacy of intrapleural fibrinolytic therapy, as measured by radiological improvement, pleural fluid drainage, inflammatory marker reduction, and requirement for surgical intervention, differs between patients with tuberculous pleural effusion and non-tuberculous pleural infection.
2. The safety profile and treatment-related adverse events, including bleeding complications, pain requiring analgesia, and secondary pleural infection following IPFT treatment, differs between patients with tuberculous pleural effusion and those with non-tuberculous pleural infection.

3.2 Significance of Research

The findings of this study are expected to have important clinical, institutional, and academic implications. Clinically, this research will provide evidence on the efficacy and safety of IPFT in the management of TPE, and determine whether efficacy, safety and treatment outcomes are comparable to those observed in non-tuberculous pleural effusions. This may support the use of IPFT as an effective adjunctive therapy in complicated TPE, potentially improvement in clinical symptoms, procedure-related complications, and the need for surgical intervention. Even as a retrospective analysis, this study offers several novel

contributions. It provides the first direct comparison of IPFT in tuberculous pleural effusion versus non-tuberculous pleural effusion, addressing a critical gap since most literature focuses on NTPE or general pleural infections.

From an institutional perspective, the results of this study may contribute to the development of evidence-based pleural management protocols at HCTM. Standardizing the approach to the management of complicated pleural effusions may improve clinical decision making, optimize resource utilization, and enhance overall patient care. In addition, this study will provide valuable local epidemiological data on the demographic profiles, clinical characteristics, and management outcomes of patients with TPE in a Malaysian tertiary care centre. Such data remain limited in the local literature and may help address an important knowledge gap in the national context. Moreover, these findings will provide a foundation for future studies, including sample size planning, optimal dosing, and safety monitoring for prospective trials or RCTs.

From a patient perspective, improved understanding of the role of IPFT in TPE may lead to more effective treatment strategies, resulting in faster recovery, improved clinical outcomes, fewer procedure-related complications, and a reduced need for surgical intervention.

CHAPTER 4

RESEARCH METHODOLOGY

4.1 Type of Study

This is a single-centre, retrospective study involving patients diagnosed with tuberculous pleural effusion and non-tuberculous pleural infection who received intrapleural fibrinolytic therapy using tissue plasminogen activator and deoxyribonuclease at Hospital Canselor Tuanku Muhriz.

4.2 Study Design

4.2.1 Period of Study

Data Collection period from 1st Jan 2016 – 31th Dec 2025 (10 years)

4.2.2 Study Setting

This study will be conducted at the Department of Internal Medicine, Hospital Canselor Tuanku Muhriz.

4.2.3 Sampling Population

All adult patients diagnosed with tuberculous pleural effusion and non-tuberculous pleural effusion who received IPFT using tissue plasminogen activator and deoxyribonuclease, during the study period. Relevant data will be extracted from patients' case notes or electronic medical records.

4.2.4. Type of Sampling

Consecutive sampling will be employed.

4.2.5 Inclusion criteria

1. Age ≥ 18 years.
2. Patient categorization and confirmation of TPE based on a composite reference standard (clinical, laboratory, histopathologic, and radiologic evaluations):

    a) **Definitive TPE**: Diagnosis established based on clinical presentation and radiological findings, with bacteriological and/or histopathological confirmation of *Mycobacterium tuberculosis* pleural infection. Confirmed tuberculous pleural infection, established by one or more of the following:

    - Positive pleural fluid acid-fast bacilli smear.
    - Positive pleural fluid GeneXpert for Mycobacterium tuberculosis.
    - Positive pleural fluid TB culture.
    - Positive pleural fluid TB PCR.
    - Histopathology from pleural biopsy consistent with TB.

    b) **Clinical TPE**: Diagnosis made based on patients without microbiological or histopathological confirmation but diagnosed by a respiratory physician based on clinical, radiological, biochemical, and/or pleuroscopic findings. Diagnosis requires at least two supportive criteria: compatible TB symptoms, radiological features suggestive of pleural TB, pleural fluid ADA >40 U/L, pleuroscopy findings suggestive of tuberculous pleuritis (e.g., pleural nodularity, inflammation, thickening, adhesions, or granulomatous changes), and/or clinical or radiological improvement following empirical anti-tuberculosis therapy.

    c) **Non-TPE**: Pleural effusion in patients with no compatible clinical presentation, radiological findings, microbiological, or histopathological evidence of *Mycobacterium tuberculosis* infection, in whom an alternative diagnosis has been established.

4.2.6 Received intrapleural fibrinolytic therapy with tissue plasminogen activator and deoxyribonuclease during the study period.

4.2.7 Exclusion Criteria

1. Malignant and transudative pleural effusion

2. Patients who received intrapleural fibrinolytic therapy as monotherapy with either tissue plasminogen activator or deoxyribonuclease alone.

3. Incomplete medical records

4.3 Study Protocol and Data Acquisition

This is a single-centre, retrospective observational cohort study conducted at the Department of Internal Medicine, Hospital Canselor Tuanku Muhriz. The study includes adult patients (≥18 years) admitted with tuberculous pleural effusion or non-tuberculous pleural effusion who received intrapleural fibrinolytic therapy between 1 Jan 2016 and 31 Dec 2025. Consecutive sampling will be used to include all eligible patients with complete medical records. To ensure confidentiality, all patient information will be anonymized and assigned unique study identification numbers. Data will be systematically extracted from multiple institutional sources, including electronic medical records, Bed Head Tickets, Radiology Information System, and Laboratory Information System, using a predefined data extraction sheet.

Data quality will be verified through cross-checking by a second investigator. Patients will be categorized into two groups based on the type of pleural effusion. The TPE group includes patients with Definite TPE and Clinical TPE, while the non-TPE group comprises those with pleural infection who do not meet the criteria for TPE. Both groups include patients who received IPFT using tissue plasminogen activator and deoxyribonuclease, with the intervention group consisting of TPE patients and the control group of non-TPE patients.

The variables collected include demographic characteristics (e.g., age, sex, and race), clinical symptoms (e.g., fever, cough and pleuritic chest pain), and comorbidities (e.g., diabetes, hypertension, chronic lung disease and Human Immunodeficiency Virus infection). Laboratory investigations include blood parameters (white blood cell count, haemoglobin level, serum protein, lactate dehydrogenase, and C-reactive protein) and pleural fluid analyses (lymphocyte count, protein, LDH, adenosine deaminase, AFB direct smear, TB culture, TB PCR and GeneXpert for Mycobacterium tuberculosis). Radiological evaluations include chest X-ray to assess effusion size and opacity.

Treatment details, including the type of fibrinolytic agent, number of doses, dosage, frequency, and duration, will also be collected. Decisions regarding completion of therapy and chest tube removal will be recorded.

Clinical outcomes will include radiological improvement or resolution of effusion from baseline prior IPFT treatment Day 0 to Day 7–10 following IPFT treatment, pleural fluid drainage within first 24 hours post-IPFT and total pleural drainage prior chest tube removal, requirement for surgical interventions such as video-assisted thoracoscopic surgery or decortication, and treatment-related adverse reaction including bleeding, pleuritic chest pain required analgesic or secondary infection following IPFT treatment.

Chest radiographs obtained before initiation of intrapleural fibrinolytic therapy (Day 0) and at Day 7–10 following therapy will be reviewed. The extent of pleural opacity will be estimated as the percentage of the affected hemithorax occupied by pleural opacity using digital chest radiographs using software available at HCTM. Two independent radiologists blinded to perform visual measurements of radiological improvement in chest X-ray. Estimated proportion of the affected hemithorax occupied by pleural opacity, including pleural effusion with or without pleural thickening, relative to the total area of the ipsilateral hemithorax, which is considered as 100%. The extent of pleural opacity will be visually estimated and recorded as a continuous percentage value ranging from 0% to 100% using a standardized assessment protocol. Radiological improvement will be calculated as the difference between the baseline and follow-up percentage pleural opacity, with a greater reduction indicating better radiological resolution.

The change in percentage pleural opacity from baseline to follow-up will be recorded as the primary radiological outcome. Interobserver agreement between the two radiologists will be evaluated using the intraclass correlation coefficient (ICC) for continuous measurements (e.g., percentage pleural opacity). An ICC $\geq$0.75 will be considered indicative of good agreement. In cases where the difference between the two measurements exceeds 10 percentage points, the radiographs will be reviewed jointly for consensus, and if consensus cannot be reached, a third independent consultant respiratory physician with expertise in pleural diseases, will adjudicate the final measurement. Data collection will be performed consistently across both TPE and Non-TPE groups, and the efficacy and safety of IPFT in TPE will be evaluated, with subgroup analyses conducted to compare clinical outcomes between the two groups.

As this is a retrospective observational study, potential confounding will be addressed through both study design and statistical adjustment. Since IPFT is administered as an adjunctive therapy for clinically indicated complicated or loculated pleural effusions, regardless of the underlying pleural disease, patients will be included only after meeting predefined indications for IPFT. Baseline clinical, biochemical, microbiological, radiological, and treatment-related variables including inflammatory markers, radiological severity, timing of antimicrobial therapy or anti-tuberculous therapy, timing of IPFT initiation, and IPFT dosing regimen, will be systematically collected. Variables considered clinically relevant or demonstrating baseline imbalance between the TPE and non-TPE groups will be adjusted using multivariable regression analyses to estimate the independent association between pleural disease type and efficacy and safety outcomes.

4.4 Operational Definitions

1. **Patient Characteristics**

a) Demographic and baseline clinical characteristics will be extracted from medical records.

b) Variables and measurement:

- **Age**: in years
- **Sex**: male / female
- **Ethnicity**: Malay / Chinese / Indian / others
- **Comorbidities**: presence of DM, HTN, CKD, COPD

a) Laboratory investigations will include both blood and pleural fluid analyses. Blood investigations will consist of white blood cell count, serum protein, lactate dehydrogenase, and total protein levels, while pleural fluid investigations will include lymphocyte count, protein, LDH, and adenosine deaminase.

b) Radiological evaluations will include Pleural effusion size on CXR using software for estimation of percentage (%) hemithorax opacity evaluated by two independent

radiologists blinded to perform measurements of radiological improvement in chest X-ray).

c) Treatment-related data will also be collected, including the timing of anti-tuberculous therapy or antibiotic therapy, number of doses fibrinolytic agent administered, and the frequency and duration of intrapleural fibrinolytic therapy.

2. Clinical symptom improvement will be assessed based on documented clinical notes in medical records as baseline, before IPFT (Day 0) and after IPFT (Day 7–10 or earlier if documented).

a) Measurement method:

- Fever: presence/absence (≥38°C documented)
- Dyspnoea: improved / no change / worse (clinical documentation)
- Cough: present/absent or improved/not improved
- Pleuritic chest pain: present/absent or improved/not improved

3. **Tuberculous Pleural Effusion**

Patient Categories and Confirmation of TPE will be categorized into three groups based on a composite reference standard, which includes clinical, laboratory, histopathologic, and radiologic evaluations:

a. **Group 1: Definite TPE**: Patients with at least one positive result from MTB culture, AFB smear, or Xpert MTB from pleural fluid or biopsy specimens, and/or histopathological evidence of caseating granulomatous inflammation suggestive of TB on pleural biopsy tissue.

b. **Group 2: Clinical TPE**: Patients who did not fulfil microbiological (positive pleural fluid AFB smear, culture, or molecular testing) or histopathological criteria for TPE, but were diagnosed as TPE by a respiratory physician based on clinical, radiological, and biochemical findings, with or without response to empirical anti-tuberculosis therapy. Diagnosis of clinical TPE required **at least two of the following criteria**:

- **Compatible clinical presentation**, including symptoms suggestive of tuberculosis such as fever, night sweats, weight loss, fatigue, or pleuritic chest pain.

- **Radiological findings suggestive of pleural tuberculosis**, including pleural effusion, pleural thickening, or associated pulmonary features compatible with TB.
- **Pleural fluid adenosine deaminase (ADA) level >40 U/L**.
- **Pleuroscopy findings suggestive of tuberculous pleuritis**, including; diffuse pleural inflammation, multiple pleural nodules, pleural thickening, hyperaemic and friable pleura, fibrinous adhesions or septations, with or without pleural biopsy demonstrating granulomatous inflammation.
- **Clinical and/or radiological improvement following initiation of empirical anti-tuberculosis therapy**.

c. **Group 3: Non-TPE**: Patients with pleural infection who had no microbiological or histological evidence of MTB and/or for whom an alternative diagnosis was established.

4. **Intrapleural Fibrinolytic Therapy**

a) IPFT is defined as the sequential intrapleural administration of tissue plasminogen activator (t-PA, alteplase) and DNase (Pulmozyme) via a chest tube for the treatment of loculated pleural effusions. The standard medication regimen at HCTM consists of 16 mg of t-PA and 5 mg of DNase per dose, with t-PA available in 50 mg ampoules and DNase in 2.5 mg ampoules. Each dose is diluted in 50 mL of 0.9% sodium chloride solution. The t-PA and DNase are administered sequentially and are not mixed in the same syringe. Following instillation, the chest tube is clamped for 45 minutes to allow the drug to act locally, then unclamped for 45 minutes to permit drainage; this sequence is repeated for the second agent. The number of doses and timing of administration is determined at the discretion of the treating chest physician, with a minimum interval of six hours between doses. Decisions regarding timing of therapy completion and chest tube removal are based on the physician's clinical judgment and radiological response.

5. Pleural opacity will be quantified using visual estimation of percentage hemithorax opacification.

a) **Percentage pleural opacity** is defined as the estimated proportion (%) of the

affected hemithorax occupied by pleural opacity, including pleural effusion with or without pleural thickening, as visualized on a chest radiograph. To ensure reliability and reduce measurement bias, radiographic assessment will be performed by two radiologists, independently measure the X-rays without knowing the patient group, and will be check if their measurements agree with each other. The assessment will be performed according to the following standardized protocol:

i. **Image selection**

- Only baseline and follow-up upright posteroanterior (PA) chest radiographs will be included where available. If a PA view is unavailable, an anteroposterior (AP) chest radiograph will be used and documented.

ii. **Image review**

- All radiographs will be anonymized and reviewed using the hospital Picture Archiving and Communication System (PACS) under standardized viewing conditions.

iii. **Assessors**

- Two independent consultant radiologists, blinded to the patients' clinical information, treatment allocation, and study outcomes, will independently review all chest radiographs.

iv. **Reference area**

- The ipsilateral hemithorax will be considered as **100%**, bounded by the lung apex superiorly, diaphragm inferiorly, mediastinum medially, and lateral chest wall laterally.

v. **Measurement of pleural opacity**

- Pleural opacity, including pleural effusion with or without pleural thickening, will be visually estimated as the percentage of the affected hemithorax occupied by pleural opacity.

- Underlying pulmonary parenchymal abnormalities (e.g., consolidation, cavitation, or atelectasis) will not be included in the estimation whenever they can be reliably distinguished from pleural opacity.

vi. **Recording of measurements**

- Percentage pleural opacity will be recorded as a continuous variable ranging from **0% to 100%**, in **5% increments**, using a standardized data collection form.

vii. **Radiological improvement**

- **The primary radiographic outcome will be the absolute reduction in pleural opacity (%), calculated by subtracting the baseline value from the Day 7–10 value.**
- **Radiological Improvement (%) = Baseline Percentage Pleural Opacity − Follow-up Percentage Pleural Opacity**
- A greater reduction indicates greater radiological resolution.

viii. **Interobserver agreement**

- Interobserver agreement between the two radiologists will be assessed using the intraclass correlation coefficient (ICC).
- An ICC ≥0.75 will be considered indicative of good agreement.

ix. **Discrepancy resolution**

- If the difference between the two assessments exceeds **10 percentage points**, the radiographs will be reviewed jointly to achieve consensus. If consensus cannot be reached, a **third independent consultant respiratory physician with expertise in pleural diseases**, who is also blinded to the patients' clinical information, treatment allocation, and study outcomes, will adjudicate the final measurement.

6. **Clinical Outcomes**

a. **Clinical symptoms improvement:** Defined as resolution or reduction of clinical symptoms, including fever, shortness of breath, and pleuritic chest pain, from baseline (Day 0, before initiation of IPFT) to Day 7–10 after initiation of IPFT or at the time of hospital discharge, whichever occurs earlier. Symptom status will be based on documented clinical assessment in medical records and classified as improved, unchanged, or worsened.

b. **Pleural fluid drainage volume:** Defined as total pleural fluid drainage volume (mL), measured as the cumulative volume drained via the pleural catheter following initiation of IPFT. This includes:

i. Drainage volume during the first 24 hours after the initial IPFT dose, and

ii. Total cumulative drainage volume from initiation of IPFT until chest tube removal.

c. **Reduction in inflammatory markers:** Defined as change in inflammatory markers, defined as the difference in serum C-reactive protein (CRP) (mg/L) and total white blood cell (WBC) count ($\times 10^9$/L) between baseline (Day 0, before initiation of IPFT) and Day 7–10 after initiation of IPFT.

d. **Requirement for surgical intervention:** Defined as the need for video-assisted thoracoscopic surgery or open decortication within 30 days following initiation of IPFT due to failure of medical management, as documented in the medical record.

e. **Treatment-related adverse events:** Defined as the occurrence of one or more of the following during or after IPFT administration until hospital discharge:

i. **Chest pain requiring analgesic treatment**, defined as new-onset or worsening chest pain occurring during or after IPFT administration that required administration of analgesic medication, as documented in the medical records.

ii. **Pleural bleeding or haemothorax**, defined as clinically significant pleural bleeding after IPFT, evidenced by haemorrhagic pleural drainage with a significant reduction in haemoglobin requiring clinical intervention (e.g., blood transfusion), or clinician-documented haemothorax.

iii. **Secondary pleural infection**, defined as a new pleural infection developing after initiation of IPFT, confirmed by positive pleural fluid microbiological culture or documented clinical diagnosis requiring additional antimicrobial therapy or pleural intervention (need for additional pleural drainage).

7. **Predictors of Poor Outcomes**

a) Factors associated with poor outcomes include advanced age, presence of comorbidities, delayed improvement in clinical symptoms, delayed radiological resolution, delayed normalization of biochemical markers (e.g., white blood cell count and C-reactive protein), requirement for surgical intervention, and the development of procedure-related complications.

b) Treatment outcomes will be assessed at two predefined time points: Day 7-10 and Day 30 following the initial intervention.

i. **Treatment Success (Day 7-10):** Defined as fulfilment of all the following criteria:

i. Adequate pleural drainage, evidenced by satisfactory fluid output and/or radiological improvement;

ii. ≥50% reduction in pleural opacity on chest radiograph compared to baseline, as determined by the reporting clinician/radiologist; and

iii. Improvement in inflammatory markers, defined as a downward trend in C-reactive protein and/or white blood cell count.

ii. **Treatment Failure (Day 7-10):** Defined as failure to meet one or more of the above criteria, including inadequate pleural drainage, <50% reduction in radiographic opacity, or lack of improvement/worsening of inflammatory markers.

iii. **Treatment Success (Day 30):** Defined as avoidance of escalation to surgical intervention (e.g., video-assisted thoracoscopic surgery or decortication) within 30 days of the initial IPFT.

iv. **Treatment Failure (Day 30):** Defined as the requirement for surgical intervention within 30 days and/or persistence or recurrence of pleural infection requiring additional invasive procedures (e.g., repeat chest tube

insertion).

v. **Treatment-related mortality** is defined as any death occurring within 30 days of the initial intervention that is directly attributable to the pleural infection or its management. This includes deaths due to sepsis, empyema-related complications, procedure-related complications, or adverse effects of therapy. Attribution will be determined by the study investigators based on clinical records. Deaths clearly due to unrelated causes will not be classified as treatment-related mortality.

4.5 Sample Size

All adult patients (≥18 years) admitted to Hospital Canselor Tuanku Muhriz between 1st Jan 2016 and 31th Dec 2025 with tuberculous pleural effusion or non-tuberculous pleural effusion who received intrapleural fibrinolytic therapy and had complete medical records will be included. Due to the absence of published studies comparing intrapleural fibrinolytic therapy in tuberculous versus non-tuberculous pleural effusions, expert clinical input and previous observational data in pleural infection were considered to guide exploratory comparisons of efficacy and safety outcomes. These were used to inform exploratory power analyses for comparative outcomes.

Sample size estimation was performed using the proportion comparison function in the Wan Nor Arifin web-based sample size calculator to estimate the number of participants required for comparing treatment success between two independent groups. As no published studies have directly compared the efficacy of IPFT in TPE and non-tuberculous pleural effusion, an exploratory treatment success rate of 100% for the TPE group was assumed based on local expert clinical opinion, while the treatment success rate for the NTPI group was derived from published literature (85.5%). Assuming a 1:3 TPE: Non-TPE allocation ratio, a two-sided significance level (α) of 0.05, and 80% statistical power, the estimated sample size required was approximately 40 patients with TPE and 120 patients with non-TPE. The unequal allocation ratio was selected because non-tuberculous pleural infections requiring intrapleural fibrinolytic therapy are expected to occur more frequently than TPE at HCTM. Given the retrospective study design and the uncertainty regarding the true effect size in tuberculous pleural effusion (TPE), all eligible patients who meet the inclusion criteria between 1 January 2016 and 31 December 2025 will be included. A post hoc power analysis will be performed to evaluate whether the available sample size is sufficient to detect clinically meaningful

differences.

Baseline clinical, radiological, and biochemical characteristics will be compared between the study groups. Variables that are clinically relevant or demonstrate statistically significant baseline imbalances will be incorporated into multivariable regression analyses to determine the independent association between pleural disease type and study outcomes.

Potential confounders to be adjusted for include baseline inflammatory markers, radiological severity, timing of initiation of anti-tuberculous therapy or antibiotic therapy, and IPFT treatment characteristics.

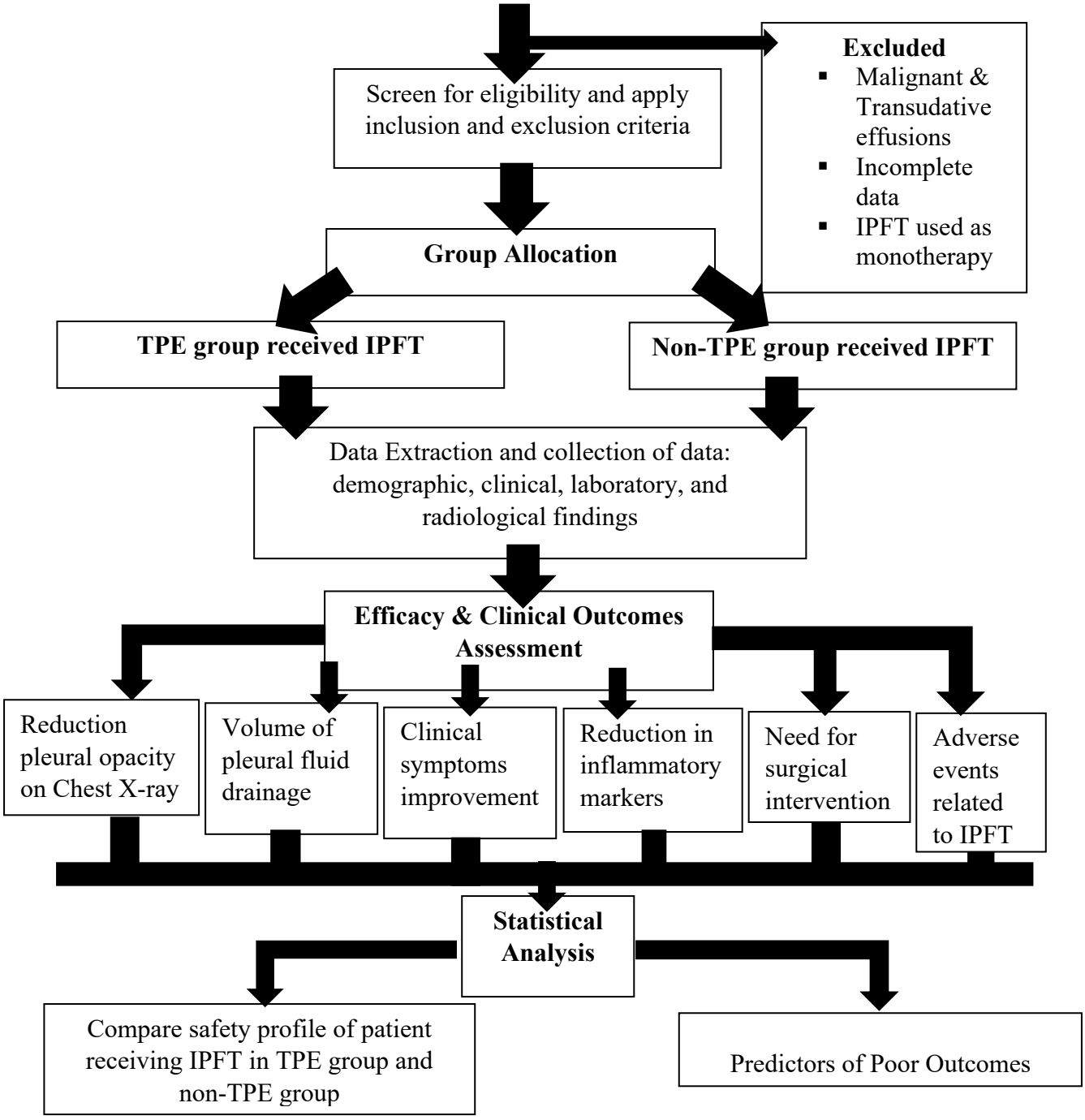
4.6 Data Collection Method

Data will be extracted from EMR, BHT, RIS, LIS using a pre-defined data collection sheet, and the casemix database managed by the International Training Centre for Casemix and Clinical Coding (ITCC), Universiti Kebangsaan Malaysia. Casemix data were used to facilitate patient identification and retrieval of relevant hospital admission records in accordance with the study inclusion and exclusion criteria. All data were accessed with the necessary institutional approvals and handled in accordance with applicable ethical and confidentiality requirements. The authors acknowledge the International Training Centre for Casemix and Clinical Coding (ITCC), Universiti Kebangsaan Malaysia, as one of the data sources for this research. Each patient will be assigned a unique study ID to ensure confidentiality. Variables include demographic and clinical characteristics, laboratory and radiological findings, treatment details, and clinical outcomes. Data will then be analysed to evaluate the efficacy and safety of IPFT in TPE compared with non-TPE and to identify predictors of poor outcomes.

4.7 Data Collection Pathway

Review medical records from electronic medical records and physical case files of patients admitted with TB pleural effusion and non-TB pleural effusion

(1st Jan 2016- 31th Dec 2025)



4.8 Statistical Analysis

Data will be analysed using Statistical Package for the Social Sciences (SPSS) version 30.0 or equivalent software.

1. Descriptive statistics will be used to summarize the study variables:
    - Categorical variables will be presented as frequencies and percentages.
    - Continuous variables will be assessed for normality using the Shapiro-Wilk test. Normally distributed variables will be presented as mean ± standard deviation (SD), while non-normally distributed variables will be presented as median with interquartile range (IQR).
2. Bivariate analysis will be performed to examine associations between baseline characteristics and clinical outcomes:
    - Chi-square test or Fisher's exact test will be used for categorical variables.
    - Independent t-test or Mann-Whitney U test will be applied for continuous variables, depending on the distribution.
3. Potential confounders include baseline inflammatory markers, radiological severity, timing of anti-tuberculous therapy or antibiotic therapy, and IPFT treatment characteristics with significant baseline differences will be included in multivariable regression analyses to determine the independent association between pleural disease type and study outcomes.
4. Multivariate analysis will be conducted to identify independent predictors of clinical outcomes:
    - Variables with $p < 0.1$ in bivariate analysis will be entered into a binary logistic regression model.
    - Adjusted odds ratios (OR) with 95% confidence intervals (CI) will be reported for all significant predictors.
5. Statistical significance will be defined as $p < 0.05$.

4.9 Dummy Table

Table 1: Demographic profile of TPE patients

Parameter	Category
Age Group	> 18- 39 years ☐ 40-59 years ☐ > 60 years ☐
Gender	Male ☐ Female ☐
Race	Malay ☐ Chinese ☐ Indian ☐ Others ☐
Diabetes Mellitus	Yes ☐ No ☐
Hypertension	Yes ☐ No ☐
Human Immunodeficiency Virus infection	Yes ☐ No ☐
Smoking	Yes ☐ No ☐

Table 2: Clinical Presentation of TPE Patients

Variable	Category
Fever	Yes ☐ No ☐
Cough	Yes ☐ No ☐
Shortness of Breath	Yes ☐ No ☐
Pleuritic Chest Pain	Yes ☐ No ☐
Weight loss	Yes ☐ No ☐
Dyspnoea	Yes ☐ No ☐

Table 3: Laboratory test results of TPE and non-TPE patients

Variable	Categories	
	TPE	Non- TPE
White cell counts, $\times 10^9$/L	<4000 ☐ >11000 ☐	<4000 ☐ >11000 ☐
Haemoglobin level, g/dL	< 11 ☐ >11 ☐	<11 ☐ >11 ☐
Serum Protein, g/L	<80 ☐ >80 ☐	< 80 ☐ >80 ☐
Serum LDH, U/L	< 250 ☐ >250 ☐	<250 ☐ >250 ☐

Table 4: Pleural Fluid Analysis TPE patients

Pleural Fluid for AFB (Direct Smear)	**Positive ☐ Negative ☐**
Pleural Fluid for AFB (Culture & Sensitivity)	**Positive ☐ Negative ☐**
Pleural fluid TB PCR	**Positive ☐ Negative ☐**
Pleural Fluid for GeneXpert MTB/RIF assay	**Positive ☐ Negative ☐**
Pleural ADA (U/L)	**< 40 ☐ > 40 ☐**
Pleural Fluid Lymphocytes, cells/ml	**< 1000 ☐ > 1000 ☐**
Pleural Fluid Protein, g/L	**<30 ☐ >30 ☐**
Pleural Fluid LDH, U/L	**<200 ☐ >200 ☐**

Table 5: Radiological Parameters of TPE patients

Variable	Categories
Baseline Chest X-ray Findings	**Right Effusion ☐** **Left Effusion ☐** **Bilateral Pleural Effusion ☐** **Consolidation ☐** **Fibrosis ☐** **Cavitation ☐**

Table 6: Diagnostic Grouping of Pleural Effusions

Variable	Categories
TPE	Definite TPE ☐ Clinical TPE ☐
Non TPE	

Table 7: Improvement in Pleural Opacity (%)

Hemithorax opacity (%)	TPE	Non-TPE
Pleural opacity (Day 0)		
Pleural opacity (Day 7–10)		
Pleural opacity reduction		

Table 8: IPFT administration of TPE and Non-TPE patients

IPFT administration	TPE	Non-TPE
Number of IPFT doses and Frequency		
Duration of IPFT (Days)		
Timing from chest tube insertion to first dose of IPFT (Days)		
Timing of IPFT initiation relative to diagnosis (Days)		
Timing of antibiotic/ATT initiation (Days from admission)		

Table 9: Volume of Pleural Fluid Drainage in TPE and Non-TPE patients

Volume of Pleural Fluid Drainage (mL)	TPE	Non-TPE
24-hour drainage volume		
Total drainage volume		

Table 10: Inflammatory Markers in TPE and Non-TPE patients

Inflammatory Markers	TPE	Non-TPE
CRP (Day 0) mg/dL		
CRP (Day 7–10) mg/dL		
WBC (Day 0) $\times 10^9$/L		
WBC (Day 7–10) $\times 10^9$/L		

Table 11: Clinical Outcomes and IPFT related Adverse event

Clinical outcome and IPFT related Adverse event	TPE	Non-TPE
Surgical intervention within 30 days	Yes ☐ No ☐	Yes ☐ No ☐
Chest pain requiring analgesia	Yes ☐ No ☐	Yes ☐ No ☐
Haemothorax	Yes ☐ No ☐	Yes ☐ No ☐
Secondary pleural infection	Yes ☐ No ☐	Yes ☐ No ☐

Table 12: Treatment Outcomes

Treatment Outcomes	TPE	Non-TPE
Treatment success (Day 7–10)	Yes ☐ No ☐	Yes ☐ No ☐
Treatment failure (Day 7–10)	Yes ☐ No ☐	Yes ☐ No ☐
Treatment success (Day 30)	Yes ☐ No ☐	Yes ☐ No ☐
Treatment failure (Day 30)	Yes ☐ No ☐	Yes ☐ No ☐

Table: Predictors of Poor Outcome

Predictors of Poor Outcome	TPE	Non-TPE
Delayed clinical improvement	Yes ☐ No ☐	Yes ☐ No ☐
Delayed radiological resolution	Yes ☐ No ☐	Yes ☐ No ☐
Delayed CRP normalization	Yes ☐ No ☐	Yes ☐ No ☐
Delayed WBC normalization	Yes ☐ No ☐	Yes ☐ No ☐

CHAPTER 5

RESEARCH ETHICS

This study will be conducted in accordance with the principles of the Declaration of Helsinki and the Malaysian Guidelines for Good Clinical Practice (GCP). Ethical approval will be sought from the Research Ethics Committee of Universiti Kebangsaan Malaysia and the Hospital Canselor Tuanku Muhriz Medical Research & Ethics Committee prior to data collection.

Patient confidentiality will be strictly maintained. All data collected during the study will be treated with the utmost confidentiality and will be accessible only to authorized members of the research team. Moreover, all data will be de-identified and stored securely in password-protected electronic databases accessible only to the research team. Since this is a retrospective study using medical records, informed consent may be waived; however, all efforts will be made to ensure patient privacy and anonymity.

CHAPTER 6

FINANCIAL PLANS

The study will utilize existing medical records, and no additional costs are anticipated.

CHAPTER 7

GANTT CHART

Progression/Timeline	Feb-March 2026	Apr-May 2026	Jun- Jul 2026	Aug-Oct 2026	Nov 2026
Literature review and proposal writing					
Proposal submission and correction					
Ethics committee approval					
Medical record review & data collection					
Statistical analysis and preparation of result					
Manuscript writing and submission					

CHAPTER 8

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