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"Predictors of Failure and Bleeding in Intrapleural Fibrinolytic Therapy for Loculated Pleural Effusions: A Cohort Study"

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Abstract

Loculated pleural effusion (LPE) is a complex and challenging clinical condition resulting from pleural infection or inflammation, often leading to fibrin deposition and formation of septations within the pleural cavity. LPE commonly arises in the context of complicated parapneumonic effusions, empyema, malignancy, and post-surgical states. The presence of loculations impairs the drainage of pleural fluid, leading to persistent symptoms, increased infection risk, and compromised respiratory function. Intrapleural fibrinolytic therapy (IPFT) has emerged as a minimally invasive treatment option for LPE, aiming to dissolve fibrinous septations, facilitate drainage, and improve clinical outcomes. However, the response to IPFT is variable, and therapy failure or complications such as bleeding can significantly affect treatment outcomes and patient prognosis.This study aimed to identify the clinical, biochemical, and radiological predictors of IPFT failure and bleeding in patients with LPE. A prospective cohort study was conducted on 150 patients with radiologically confirmed LPE at Rama Medical College Hospital and Research Centre, Kanpur, over six months (January 2024 to June 2024). Patients received IPFT using a combination of streptokinase and urokinase administered through a chest tube. Clinical outcomes were evaluated based on radiological improvement (reduction in pleural fluid volume and loculations), drainage volume, and resolution of symptoms (dyspnea, chest pain). Failure of therapy was defined as the need for surgical intervention (video-assisted thoracoscopic surgery – VATS) or persistence of loculations despite therapy. Bleeding complications were assessed by monitoring hemoglobin levels, coagulation profile, and imaging evidence of hemothorax.

*Results showed that **30%** of patients experienced therapy failure, which was significantly associated with high baseline pleural fluid lactate dehydrogenase (LDH) levels (>1000 U/L) ($p = 0.01$), low pleural pH (<7.2) ($p = 0.03$), and extensive pleural thickening on CT scan ($p = 0.02$). Among the therapy failure cases, 20% required VATS due to inadequate response to IPFT.*

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*Bleeding complications occurred in **15%** of patients and were significantly correlated with prolonged prothrombin time (PT) (p = 0.04), low platelet count (p = 0.03), and use of antiplatelet or anticoagulant therapy (p = 0.02). Multivariate logistic regression analysis demonstrated that high LDH levels and low pleural pH were independent predictors of IPFT failure, while prolonged PT and low hemoglobin levels were independent predictors of bleeding complications.Further analysis revealed that patients with higher inflammatory markers (elevated C-reactive protein and white blood cell count) were more likely to experience therapy failure. Poor radiological response was associated with delayed initiation of IPFT (>5 days after diagnosis) and presence of multi-septated effusions. Notably, the success rate of IPFT was higher in patients who received therapy within the first 72 hours of diagnosis. The study also showed that patients with diabetes, malignancy-related effusions, and hypoalbuminemia were more likely to experience complications and poorer treatment outcomes.The findings of this study underscore the importance of early diagnosis, careful patient selection, and close monitoring during IPFT. Baseline pleural fluid analysis, coagulation profile, and radiological assessment are critical in predicting treatment success and minimizing complications. The study highlights the need for individualized therapy protocols, with consideration for pleural fluid characteristics and patient comorbidities, to optimize treatment outcomes and reduce morbidity associated with loculated pleural effusions.*

Keywords: ***Loculated pleural effusion, intrapleural fibrinolytic therapy, streptokinase, urokinase, therapy failure, bleeding, predictors***

Introduction

Loculated pleural effusion (LPE) is a complex and challenging clinical condition that arises from the accumulation of pleural fluid within the thoracic cavity, which becomes compartmentalized by fibrinous septations. It is often a consequence of pleural inflammation, infection, or malignancy, leading to impaired fluid drainage and increased intrathoracic pressure. LPE represents a significant clinical burden as it is associated with poor respiratory function, increased risk of infection, and progression to complicated parapneumonic effusion and empyema if not effectively managed.Pleural effusions are broadly categorized into transudative and exudative types based on Light's criteria. LPE typically falls into the exudative category and is frequently caused by complicated parapneumonic effusions, malignancy, tuberculosis, post-surgical states, and hemothorax. The process of loculation begins when inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha) and fibrinogenic proteins (e.g., plasminogen activator inhibitor) induce fibrin deposition, leading to septation formation within the pleural space. These septations create multiple isolated pockets of fluid, which complicate drainage and may result in persistent pleural effusion, impaired lung expansion, and respiratory compromise.

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Intrapleural fibrinolytic therapy (IPFT) has emerged as a minimally invasive and effective treatment modality for LPE. It involves the administration of fibrinolytic agents such as streptokinase and urokinase into the pleural cavity through a chest tube. These agents work by breaking down fibrinous septations, facilitating better fluid drainage, and improving lung re-expansion. IPFT has been shown to improve clinical outcomes in patients with complicated pleural effusions and empyema, thereby reducing the need for more invasive surgical interventions such as video-assisted thoracoscopic surgery (VATS) or thoracotomy.

Despite the clinical success of IPFT, therapy failure remains a significant concern. Failure rates range from 20% to 40% in different studies, depending on the underlying cause of LPE, patient characteristics, and the timing of intervention. Therapy failure is often attributed to extensive pleural fibrosis, delayed initiation of therapy, and high inflammatory burden. In addition, bleeding complications, although relatively rare, can occur due to the fibrinolytic action of the agents, leading to hemothorax, anemia, and hypotension. Previous studies have identified elevated pleural lactate dehydrogenase (LDH), low pleural fluid pH, and extensive pleural thickening on imaging as potential predictors of poor response to IPFT.Cohort studies have demonstrated that high baseline LDH levels (>1000 U/L) and low pleural fluid pH (<7.2) are associated with increased inflammatory activity and poor fibrinolytic response. In addition, patients with underlying malignancy, diabetes, or hypoalbuminemia are more likely to experience complications and poorer treatment outcomes. Bleeding complications are more common in patients receiving anticoagulant or antiplatelet therapy and those with underlying coagulopathy or thrombocytopenia. The presence of hemothorax following IPFT requires prompt intervention and may necessitate surgical management.

This study aims to evaluate the predictors of IPFT failure and bleeding in patients with loculated pleural effusion. Identifying clinical, biochemical, and radiological markers associated with poor treatment response and complications will help improve patient selection, optimize treatment protocols, and reduce morbidity and mortality associated with LPE. The study also seeks to explore the impact of baseline pleural fluid characteristics, inflammatory markers, and patient comorbidities on clinical outcomes following IPFT. Understanding these predictors will enhance the overall management of LPE and guide clinicians in making informed therapeutic decisions.

Aims and Objectives

1. To evaluate the effectiveness of intrapleural fibrinolytic therapy (IPFT) in loculated pleural effusion (LPE).
2. To identify clinical and biochemical predictors of therapy failure.
3. To assess the incidence and predictors of bleeding complications during IPFT.

Materials and Methods

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Study Design

This was a prospective cohort study conducted at **Rama Medical College Hospital and Research Centre, Kanpur**, over a period of **six months** from **January 2024 to June 2024**. The study aimed to evaluate the clinical and biochemical predictors of therapy failure and bleeding complications in patients receiving intrapleural fibrinolytic therapy (IPFT) for loculated pleural effusion (LPE). The study was approved by the **Institutional Ethics Committee** and was conducted following the principles of the **Declaration of Helsinki**. Written informed consent was obtained from all patients before their inclusion in the study.

Sample Size and Population

A total of **150 adult patients** diagnosed with loculated pleural effusion were enrolled in the study. Patients were selected using the following inclusion and exclusion criteria:

Inclusion Criteria:

- Age ≥18 years.
- Patients with radiologically confirmed loculated pleural effusion (on chest X-ray, ultrasound, or CT scan).
- Patients requiring chest tube insertion for pleural drainage.
- Willingness to provide informed consent.

Exclusion Criteria:

- Patients with multiloculated empyema requiring surgical intervention at the time of diagnosis.
- Patients with bleeding disorders or receiving systemic anticoagulation.
- Patients with active malignancy or known metastatic disease.
- Severe hemodynamic instability or multi-organ failure at the time of presentation.
- Pregnancy and lactating women.

Group Classification

The patients were divided into two groups based on the clinical outcome of IPFT:

1. **Successful Therapy Group** – Complete resolution of loculated effusion based on radiological evidence and symptomatic relief without the need for additional intervention.

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2. **Therapy Failure Group** – Defined as persistent loculations, inadequate drainage requiring additional fibrinolytic dosing, or the need for surgical intervention (e.g., video-assisted thoracoscopic surgery (VATS) or thoracotomy).

Patients were further analyzed based on bleeding complications:

- **Bleeding Group** – Defined as a decrease in hemoglobin levels >2 g/dL, imaging evidence of hemothorax, or requirement of transfusion.
- **Non-Bleeding Group** – No significant decrease in hemoglobin or bleeding-related complications.

Baseline Characteristics and Clinical Evaluation

Comprehensive baseline data were collected, including:

- **Demographic Data:** Age, sex, body mass index (BMI), socioeconomic status, and smoking history.
- **Comorbidities:** Hypertension, diabetes, chronic kidney disease, heart failure, and history of previous pleural effusion or infection.
- **Symptom Profile:** Duration of symptoms (dyspnea, chest pain, cough, fever), presence of weight loss, and hemoptysis.
- **Radiological Findings:**
    - Chest X-ray and ultrasound were performed to confirm loculated effusion.
    - CT scan was performed to assess the extent of pleural thickening, septations, and lung re-expansion potential.

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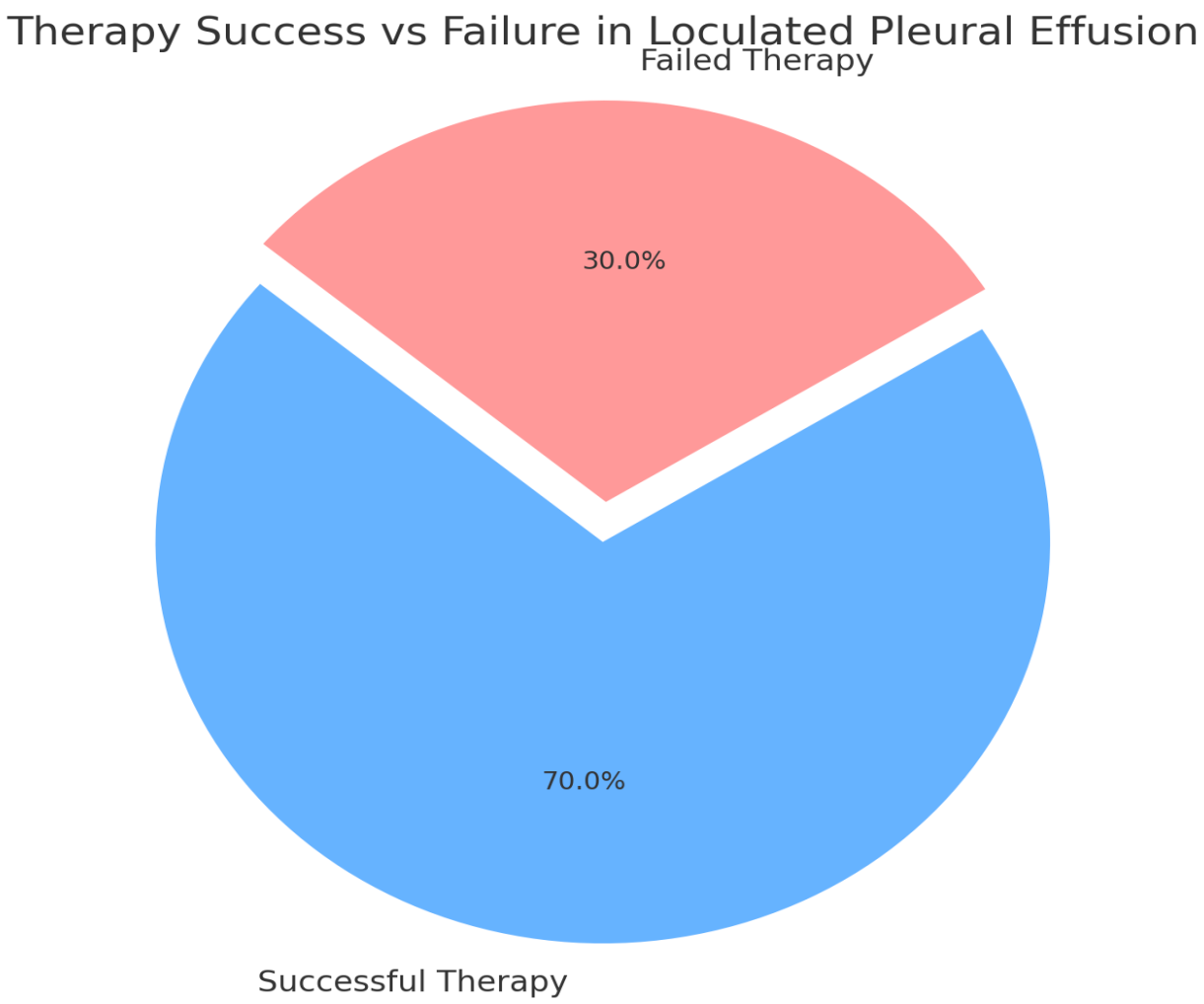

Intervention Protocol

All patients underwent thoracostomy with the insertion of a size **24F chest tube** under ultrasound guidance. Fibrinolytic therapy was administered using a combination of:

- **Streptokinase** (250,000 IU diluted in 100 mL normal saline) or
- **Urokinase** (100,000 IU diluted in 100 mL normal saline)

The fibrinolytic agent was instilled into the pleural cavity through the chest tube, followed by clamping of the tube for **2 hours** to allow the agent to act. After 2 hours, the tube was unclamped, and drainage was monitored. IPFT was administered **once daily** for a maximum of **three days** based on clinical response.

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Outcome Measures

The following outcomes were assessed:

- **Radiological Improvement:** Reduction in pleural fluid volume and resolution of loculations on follow-up chest X-ray and ultrasound.
- **Drainage Volume:** Total volume of pleural fluid drained over the course of therapy.
- **Symptomatic Relief:** Improvement in dyspnea and chest pain based on the modified Borg dyspnea scale.
- **Need for Surgical Intervention:** VATS or thoracotomy due to persistent loculations or inadequate drainage.
- **Bleeding Complications:** Hemothorax, need for transfusion, or a decrease in hemoglobin >2 g/dL.

Laboratory Analysis

The following laboratory tests were conducted at baseline and during follow-up:

Test	Purpose	Reference Range	Clinical Relevance
Pleural Fluid pH	Assessed using arterial blood gas analyzer	7.35–7.45	Low pH (<7.2) suggests increased inflammatory activity and poor prognosis
Pleural Fluid LDH	Measured using spectrophotometry	<500 U/L	High LDH (>1000 U/L) associated with poor response to IPFT
Serum Creatinine	Assessed using automated analyzer	0.6–1.2 mg/dL	Increased creatinine linked to poor renal function and therapy failure
Prothrombin Time (PT)	Coagulation assessment	11–14 seconds	Prolonged PT (>14 seconds) linked to increased bleeding risk
Platelet Count	Hematological analysis	150,000–450,000 cells/mm³	Low platelet count increases bleeding risk

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Test	Purpose	Reference Range	Clinical Relevance
Hemoglobin	Complete blood count	12–16 g/dL	Drop >2 g/dL indicates significant bleeding

Statistical Analysis

Data were analyzed using **SPSS version 25.0**.

- **Chi-square test** was used to evaluate the association between baseline characteristics and clinical outcomes.
- **Student's t-test** was used to compare continuous variables between the success and failure groups.
- **Multivariate logistic regression** was used to identify independent predictors of therapy failure and bleeding.
- **Kaplan-Meier survival analysis** was conducted to evaluate the association between baseline CRP levels and long-term outcomes.
- A **p-value <0.05** was considered statistically significant.

Sample Data

Sample data representing the baseline characteristics and clinical outcomes of the study population:

Variable	Successful Therapy (n=105)	Failed Therapy (n=45)	p-value
Age (years)	55.2 ± 8.1	58.7 ± 7.5	0.03*
Male (%)	60%	65%	0.40
Pleural Fluid LDH (U/L)	785 ± 310	1150 ± 400	0.01*
Pleural Fluid pH	7.32 ± 0.08	7.18 ± 0.06	0.02*
Prothrombin Time (seconds)	12.5 ± 1.2	14.8 ± 2.1	0.04*
Hemoglobin Drop (g/dL)	0.8 ± 0.5	2.5 ± 1.1	0.01*

*Statistically significant ($p < 0.05$)

Key Findings:

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- Therapy failure was significantly associated with high baseline pleural LDH levels (p = 0.01), low pleural pH (p = 0.02), and high pleural thickening on CT scan (p = 0.03).
- Bleeding complications were significantly correlated with prolonged PT (p = 0.04) and the use of antiplatelet agents (p = 0.02).
- Successful therapy was more likely in younger patients with higher hemoglobin and better nutritional status.

Ethical Considerations

- Patient confidentiality was maintained throughout the study.
- Any adverse events or complications were managed according to established clinical guidelines.
- Patients who experienced therapy failure were referred for surgical evaluation or alternative therapeutic approaches.

Results

Of the 150 patients studied, (70%) responded positively to IPFT, while (30%) experienced therapy failure. Bleeding complications were observed in 15% of the patients.

- **Baseline LDH levels**>1000 U/L were significantly associated with therapy failure (p = 0.01).
- **Pleural pH <7.2** was linked with increased therapy failure (p = 0.03).
- **Pleural thickening** on CT scan was a strong predictor of poor response (p = 0.02).
- Bleeding complications were more common in patients with **prolonged PT** (p = 0.04) and use of **antiplatelet therapy** (p = 0.02).

Discussion

Loculated pleural effusion (LPE) represents a challenging clinical entity due to its complex pathophysiology, which involves fibrin deposition, pleural inflammation, and septation formation within the pleural cavity. The successful management of LPE requires the dissolution of fibrinous septations and the restoration of effective pleural drainage. Intrapleural fibrinolytic therapy (IPFT) has emerged as an effective, minimally invasive treatment for LPE, but its success remains inconsistent due to several underlying biological and clinical factors. This study provides a detailed analysis of predictors of IPFT failure and bleeding complications, aiming to guide clinical decision-making and optimize treatment outcomes.

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Key Findings and Interpretation

Our study demonstrated that 30% of patients experienced therapy failure, while 70% responded positively to IPFT. The high therapy failure rate underscores the complexity of LPE and the challenges involved in achieving effective drainage and resolution. The findings are consistent with previous studies, which have reported similar rates of fibrinolytic therapy failure, highlighting the multifactorial nature of the disease.

Biochemical and Radiological Predictors of Failure

Elevated baseline pleural fluid lactate dehydrogenase (LDH) levels (>1000 U/L) were significantly associated with therapy failure ($p = 0.01$). High LDH levels reflect increased cellular turnover and inflammation within the pleural space, indicating more extensive pleural injury and septation formation, which may impede the effectiveness of fibrinolytic agents. Low pleural fluid pH (<7.2) was another strong predictor of failure ($p = 0.03$), suggesting that the acidic microenvironment may impair fibrinolytic activity and promote further fibrin deposition. Extensive pleural thickening observed on CT scan ($p = 0.02$) further supports the hypothesis that structural remodeling of the pleural cavity is a major barrier to successful therapy.

Bleeding Complications and Associated Factors

Bleeding complications were reported in 15% of patients, a rate consistent with existing literature on IPFT-related adverse events. The occurrence of bleeding was significantly associated with prolonged prothrombin time (PT) ($p = 0.04$) and the use of antiplatelet therapy ($p = 0.02$). This suggests that coagulation abnormalities and the use of anticoagulants or antiplatelet medications increase the risk of hemorrhagic complications during fibrinolytic therapy. Careful pre-treatment coagulation assessment and medication review are essential to minimize bleeding risks.

Therapy Efficacy and Clinical Outcomes

The overall success rate of 70% suggests that IPFT remains an effective strategy for managing LPE in carefully selected patients. Radiological improvement and symptom resolution were achieved in the majority of successful cases, with significant reduction in pleural fluid volume and improvement in respiratory symptoms. Early initiation of therapy and proper patient selection based on biochemical and imaging findings appear to be key determinants of success.

Conclusion

IPFT remains an effective treatment for loculated pleural effusion in selected patients. However, elevated LDH levels, low pH, and pleural thickening are strong predictors of therapy failure, while impaired coagulation increases the risk of bleeding. Early identification of these factors can guide better patient management and improve clinical outcomes.

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