ORIGINAL RESEARCH

Machine Learning Model Predictors of Intrapleural Tissue Plasminogen Activator and DNase Failure in Pleural Infection
A Multicenter Study

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Abstract

Rationale: Intrapleural enzyme therapy (IET) with tissue plasminogen activator (tPA) and DNase has been shown to reduce the need for surgical intervention for complicated parapneumonic effusion/empyema (CPPE/empyema). Failure of IET may lead to delayed care and increased length of stay.

Objectives: The goal of this study was to identify risk factors for failure of IET.

Methods: We performed a multicenter, retrospective study of patients who received IET for the treatment of CPPE/empyema. Clinical and radiological variables at the time of diagnosis were included. We compared four different machine learning classifiers (L1-penalized logistic regression, support vector machine [SVM], extreme gradient boosting [XGBoost], and light gradient-boosting machine [LightGBM]) by multiple bootstrap-validated metrics, including F-β, to demonstrate model performances.

Results: A total of 466 participants who received IET for pleural infection were included from five institutions across the United States. Resolution of CPPE/empyema with IET was achieved in 78% ($n = 365$). SVM performed superiorly, with median F-β of 56%, followed by L1-penalized logistic regression, LightGBM, and XGBoost. Clinical and radiological variables were graded based on their ranked variable importance. The top two significant predictors of IET failure using SVM were the presence of an abscess/necrotizing pneumonia (17%) and pleural thickening (13%). Similarly, LightGBM identified abscess/necrotizing pneumonia (35%) and pleural thickening (26%) and XGBoost indicated pleural thickening (36%) and abscess/necrotizing pneumonia (17%) as the most significant predictors of treatment failure. Predictors identified by the L1-penalized logistic regression model were pleural thickening (18%) and pleural fluid lactate dehydrogenase (LDH) (9%).

Conclusions: The presence of abscess/necrotizing pneumonia and pleural thickening consistently ranked among the strongest predictors of IET failure in all machine learning models. The difference in rankings between models may be a consequence of the different algorithms used by each model. These results indicate that the presence of abscess/necrotizing pneumonia and pleural thickening may predict IET failure. These results should be confirmed in larger studies.

Keywords: empyema; pleural infection; complex parapneumonic effusion; intrapleural tissue plasminogen activator and DNase; intrapleural enzyme therapy

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Complicated parapneumonic effusion (CPPE) and empyema management remains challenging and is associated with significant 30-day and 1-year mortality (1). The cornerstones of management are prompt drainage of the infected pleural space and initiation of antimicrobial therapy (2). Intrapleural enzyme therapy (IET), with tissue plasminogen activator (tPA) and DNase (DNase), has been shown to break down fibrin in CPPE/empyema and facilitate drainage. IET has been shown to improve radiographic outcomes, decrease hospital length of stay, and reduce the need for surgical intervention in the MIST2 (Multi-Centre Intrapleural Sepsis 2) trial (3). This therapy has become the standard of care for management of difficult-to-drain CPPE and empyema. There is increasing evidence that demonstrates efficacy, with treatment success rates of 90% despite variation in dosage and method of administration (4–6).

Despite appropriate medical therapy, surgical intervention continues to play a crucial role in cases where pleural infection has not been effectively controlled. However, the role of surgical intervention remains unclear, with much of the debate revolving around patient selection (7, 8). In addition, patients with later stages of empyema with an organized pleural thickening are less likely to achieve lung reexpansion without surgery (9). Current guidelines recommend the use of surgery in cases of "medical treatment failure" or when an advanced fibrotic state is suspected with extensive pleural thickening (2). For patients in whom intrapleural tPA/DNase therapy is likely to fail, IET may simply delay surgical referral. It is important for clinicians to identify the patients in whom IET with tPA/DNase is likely to fail, facilitating early surgical intervention. The study used supervised machine learning with extreme gradient boosting to investigate the relative importance of predictors of IET failure among patients with pleural infection. Pleural thickening and the presence of abscess/necrotizing pneumonia have been identified as the most important predictors of IET failure in a single-center study using supervised machine learning with extreme gradient boosting (10).

Machine learning has been used to analyze large amounts of data and identify patterns that can predict outcomes in patients with respiratory disease (11). Machine learning involves training algorithms to learn from data without being explicitly programmed. Several studies have trained the algorithms on the data from electronic health records that contained information such as patient demographics, medical history, and laboratory values. The machine learning models used in these studies were able to accurately predict outcomes, such as mortality and exacerbation, in patients with respiratory disease with high accuracy, outperforming traditional scoring systems (12–14). This suggests that machine learning has the potential to improve patient outcomes by identifying high-risk patients early and developing personalized treatment plans.

To further evaluate the effectiveness of this predictive model, we performed a retrospective, multicenter study to determine the significance of candidate variables in predicting IET failure among patients with pleural infection.

Methods

Study Design

This was a retrospective multicenter study conducted in five institutions across the United States and included consecutive patients who underwent IET for CPPE/empyema management between January 2012 and February 2020. The institutional review board at each respective institution approved this study.

CPPE was defined as the presence of pleural effusion on chest computed tomography (CT) or X-ray and evidence of pleural space septation and/or loculation on thoracic ultrasonography or CT scan, with an exudative profile on pleural fluid chemistry and pleural fluid pH $\leqslant$ 7.2, whereas empyema was defined as pleural fluid that is purulent in appearance or has positive Gram stain or cultures. The success of IET with tPA/DNase was characterized by clinical and radiographic improvement, with CT imaging after IET showing complete or nearly complete resolution of the effusion. Failure was characterized by either the persistence of CPPE/empyema on chest CT or any complications that necessitated surgical intervention.

Study Population

Subjects were retrospectively identified from the hospital pharmacy database based on the presence of Current Procedural Terminology codes 32561 or 32562, indicating the use of intrapleural tPA/DNase for CPPE/empyema. Clinical variables included demographic details, underlying pulmonary conditions, chest tube size, presence of an additional chest tube, pleural fluid chemistry, inappropriate initial antibiotics (defined as those not matching the final susceptibility from pleural fluid cultures, if available), and the purulent nature of the effusion. Radiographic features analyzed included pleural thickening (>2 mm) on axial plane, an appearance of loculation, and the presence of lung abscess or necrotizing pneumonia.

Management

All patients were initially given empiric antibiotics as determined by the treating physicians and the clinical setting (community acquired or hospital acquired). Whenever possible, the antibiotics were adjusted based on culture sensitivity results. The determination of chest tube type, size, and management was entrusted to the expertise of clinicians within each respective institution. The size and the method of chest drain placement were recorded, as well as the presence of a second chest drain due to nondraining multiloculated parapneumonic effusion or need for surgery. All participating centers followed a similar regimen for IET: 10 mg of intrapleural tPA and 5 mg of intrapleural DNase. The length and frequency of treatment in each center was per discretion of the pleural disease treatment team in that institution and did not exceed a maximum of six doses of IET during the course of treatment and no more than two therapies within a 24-hour time period. All centers clamped the chest tube for 1 hour after the administration of intrapleural tPA/DNase. The administration of IET was initiated within 24–48 hours after the insertion of the chest drain.

Statistical Analysis

Simple descriptive statistics were used to describe patient demographics. Categorical variables were summarized using frequencies with percentages. Continuous variables were displayed as mean and standard deviation when normally distributed or median and interquartile range (IQR) if appropriate. The study included a total of 466 subjects who were randomly divided into training ($n = 372$) and testing ($n = 94$) sets at an 80:20 ratio. The dataset contained missing values for 5 out of 14 clinical variables, namely chest tube size, pleural fluid glucose, LDH, protein, and pH. Binary variables were created to

indicate when an observation required imputation for a given missing variable. The missing values in the dataset were imputed using the multivariate imputation by chained equations (MICE) technique and binary variables (15, 16), which involves estimating the missing values for each variable by using other variables in the dataset as predictors. This method was implemented iteratively, with each iteration improving the estimation of missing values based on information gained in the previous iteration. After imputing missing data using MICE, the resulting dataset was used for further analysis or modeling.

The training data were further divided into in-bag and out-of-bag training data (using the same ratio) for hyperparameter tuning. Adaptive optimization (tree-parzan estimator) was used to tune the hyperparameters for each of the four different machine learning classifiers: L1-penalized logistic regression, support vector machine (SVM), Extreme Gradient Boosting (XGBoost), and light gradient-boosting machine (LightGBM) to maximize out-of-bag F-β. Finally, each model was fitted to the full training data using the tuned hyperparameter values. The goal of hyperparameter tuning was to find the optimal set of hyperparameters for each classifier that maximized its performance on the out-of-bag training data. Once the hyperparameters were tuned using the out-of-bag training data, each model was fitted to the full training data using the optimal set of hyperparameters. This final step ensured that the models were trained on the complete training dataset with the optimal set of hyperparameters, which could then be used to make predictions on new data (17–20).

Once each model was tuned and fit, model performance was assessed on the testing data ($n = 94$) in terms of F-β (a weighted version of the F-1 score). To address the challenges associated with a limited sample size and to mitigate overfitting, we integrated several advanced machine learning techniques into our methodology, including cross-validation, regularization, and bootstrapping. Variable importance was estimated by random permutation to rank the importance of clinical and derived variables with respect to their influence on failure of IET. The F-1 score is the harmonic mean of precision (true predictive value) and recall (true positive rate) (21–23). In clinical practice, delaying surgical intervention in the setting of ongoing or inadequately drained pleural space infection can be harmful to the patients, which may lead to worsening sepsis or increasing risk of complications. Therefore, this study weighted recall twice as heavily as precision. In other words, we scored model performance by prioritizing recall over precision. The whole pipeline was repeated 200 times (from random split to F-β and area under the curve testing) to yield valid distributions for test metrics.

Results

We identified 466 patients with a diagnosis of CPPE/empyema who received at least one chest drain and IET. The median number of dosages was five doses (IQR, three doses). Clinical characteristics are summarized in Table 1. Among 466 patients, 37.1% ($n = 173$) received appropriate antibiotics, ensuring that the prescribed antibiotics matched the sensitivity of their microbiology culture results. Small-bore catheters (8–18 F) were placed in 413 (88.6%) patients, whereas 53 (11.4%) had large chest drains (20–32 F). Chest drains were placed percutaneously with image guidance in 438 (94%) subjects. In this cohort, 311 (67%) patients were diagnosed with empyema based on the presence of purulent effusion, positive culture or Gram stain, or acidic fluid with a pH < 7.2. Of the 311 cases, 63% ($n = 197$) had positive cultures from pleural fluid (Table 2). In the CPPE group (155 patients), effusions were considered as pleural infections based on their clinical assessment including exudative profile, low glucose (<60 mg/dl), and the presence of septations on imaging studies.

The overall success rate of IET was 78.3% ($n = 365$). Among the 101 patients

Table 1. Demographic and clinical characteristics

Demographic and Characteristics	Cohort Data ($N = 466$)	IET Success ($n = 365$)	IET Failure ($n = 101$)
Patient characteristic			
Age, yr	56.3 ± 17	56.7 ± 17	54.7 ± 16
Sex, female	178 (38.2)	140 (38.4)	38 (37.6)
Presence of COPD or ILD	83 (17.8)	70 (19.1)	13 (12.8)
Placement of second chest tube	69 (14.8)	59 (16.1)	10 (9.9)
Small-bore catheter placement (8–18 F)	413 (88.6)	331 (90.7)	82 (81.2)
Appropriate antibiotics (matched sensitivity)	173 (37.1)	131 (36)	42 (41.6)
Days from drain insertion to removal	5 (4–8)	5 (4–7)	6 (4–10)
Days from admission to discharge	12 (8–18)	11 (8–17)	15 (10–20)
Radiographic characteristics			
Evidence of loculation on CT scan	346 (74.2)	262 (71.8)	84 (82.3)
Pleural thickening (>2 mm)	130 (27.9)	87 (23.8)	43 (42.5)
Presence of abscess and/or necrotizing pneumonia	122 (26)	77 (21)	45 (44.5)
Pleural effusion characteristics			
Side of effusion, right	255 (55)	198 (54.2)	57 (56.4)
Culture positive	197 (42)	146 (40)	51 (50.4)
Presence of purulent pleural fluid	149 (32)	100 (27.4)	49 (48.5)
Pleural fluid pH	7.2 ± 0.43	7.2 ± 0.37	7.12 ± 0.44

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CT = computed tomography; IET = intrapleural enzyme therapy; ILD = interstitial lung disease.
Data are given as mean ± standard deviation, *n* (%), or median (interquartile range).

Table 2. Organisms and cultures among those with complicated parapneumonic effusion/empyema

Organisms	Cohort Data (*N* = 197)	IET Success (*n* = 145)	IET Failure (*n* = 52)
Streptococcus spp.	106 (53.8)	78 (53.8)	28 (53.8)
MRSA	26 (13.2)	20 (13.8)	6 (11.5)
MSSA	20 (10.1)	16 (11)	4 (7.7)
Other gram positive	9 (4.5)	6 (4.1)	3 (5.8)
Anaerobes	13 (6.6)	11 (7.5)	2 (3.8)
Klebsiella spp.	5 (2.5)	4 (2.8)	1 (1.9)
Escherichia coli	3 (1.5)	1 (0.7)	2 (3.8)
Pseudomonas aeruginosa	3 (1.5)	1 (0.7)	2 (3.8)
Haemophilus spp.	2 (1)	1 (0.7)	1 (1.9)
Other gram negative	3 (1.5)	2 (1.4)	1 (1.9)
Fungus	4 (2)	3 (2.1)	1 (1.9)
Mixed organisms	3 (1.5)	2 (1.4)	1 (1.9)

Definition of abbreviations: IET = intrapleural enzyme therapy; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.
Data are given as *n* (%).

who did not respond to combined intrapleural therapy, surgery was indicated for the following reasons: *1*) worsening sepsis irrespective of radiographic findings (*n* = 56); *2*) persistent infection with deteriorating follow-up chest CT (*n* = 42); or *3*) the development of hemothorax (*n* = 3). There were four candidate machine learning classifiers: *1*) SVM performed the best, with median F-β of 56% (central 95th percentile: 44–65%); followed by *2*) L1-penalized logistic regression, with median F-β 52% (central 95th percentile: 0–62%); *3*) LightGBM, with median F-β 48% (central 95th percentile: 24–66%); and *4*) XGBoost, with F-β 45% (central 95th percentile: 0–63%) (Figure 1).

The 14 clinical and radiological variables, as well as 5 imputed variables, were graded based on their ranked variable importance using machine learning models. The top two significant predictors of IET failure using SVM were the presence of an abscess and/or necrotizing pneumonia (17%) and pleural thickening (13%). Meanwhile, the most significant predictors using L1-penalized logistic regression were pleural thickening (18%) and pleural fluid LDH (9%). LightGBM identified abscess or necrotizing pneumonia (35%) and pleural thickening (26%) as the most significant predictors. Similarly, XGBoost indicated that pleural thickening (36%) and abscess or necrotizing pneumonia (17%) were the most significant predictors (Table 3). Figure 2 shows the ranked variable importance from each model.

Discussion

To our knowledge, this is the largest study to date to determine the predictors of IET failure in pleural infection. Our dataset represents the experiences of five institutions with different practice settings over an 8-year period, including two university-based and three community-based practices. We observed an overall success rate of 78.3%. In comparison, other studies have reported success rates ranging from 85% to 92% (24–27). IET has proven effective in decreasing the necessity for surgical intervention in patients with CPPE/empyema (3). However, some cases still require surgery, despite completing a complete course of IET. Identifying risk factors for the failure of combined intrapleural therapy is vital in clinical practice and may aid in identification of high-risk patients who need prompt surgical intervention instead.

In a previous retrospective study, machine learning with extreme gradient boosting was used to assess the relative importance of predictors for IET failure, identifying pleural thickening and abscess/necrotizing pneumonia as the most significant predictors (10). In this multicenter study, four machine learning models were used to rank a wide range of clinical and radiological variables that contribute to IET failure.

The presence of abscess/necrotizing pneumonia and pleural thickening consistently ranked among the top two predictors of IET failure across three machine learning models (all except

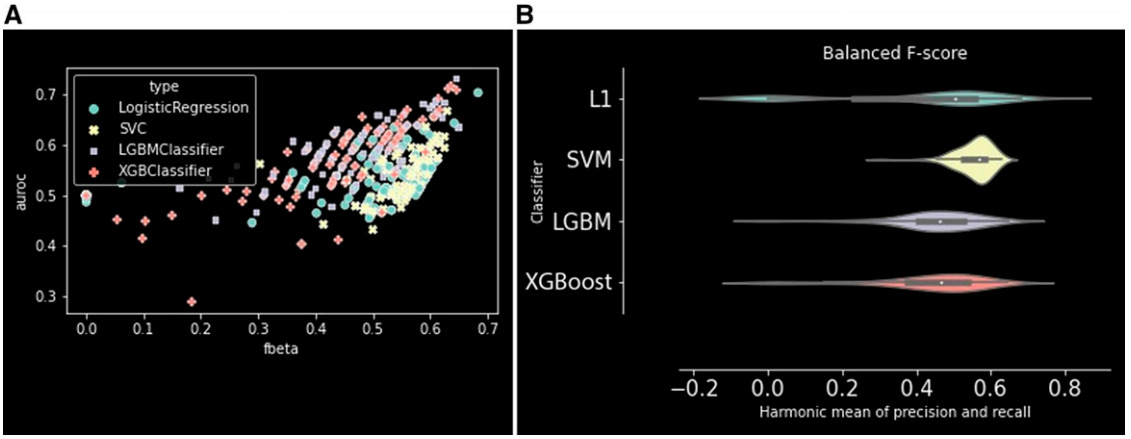

Figure 1. (*A*) Performance of machine learning models is shown on scatter plots. (*B*) Violin plot comparing the distribution of F-β across four different machine learning models. auroc = area under the receiver operating characteristic curve; L1 = L1-penalized logistic regression; LGBM = light gradient-boosting machine; SVC = support vector classification; SVM = support vector machine; XGBoost = extreme gradient boosting.

Table 3. Machine learning models and the variable importance ranking from each model

	F-β (%)	First Ranking	Second Ranking
Support vector machine	56 (44–65)	Abscess or necrotizing pneumonia (17%)	Pleural thickening (13%)
L1-penalized logistic regression	52 (0–62)	Pleural thickening (18%)	LDH pleural (9%)
Light gradient-boosting machine	48 (24–66)	Abscess or necrotizing pneumonia (35%)	Pleural thickening (26%)
XGBoost	45 (0–63)	Pleural thickening (36%)	Abscess or necrotizing pneumonia (17%)

Definition of abbreviations: LDH = lactate dehydrogenase; XGBoost = extreme gradient boosting.
The F-β score is a performance metric that assesses a model by combining precision and recall in a flexible manner. A higher F-β score indicates better model performance, reflecting a more optimal balance between precision and recall.

L1-penalized logistic regression). The different rankings between models may be attributed to the varying algorithms used by each model. These results suggest that the presence of abscess/necrotizing pneumonia and pleural thickening strongly increases the risk of intrapleural IET failure. Hence, expedited surgical management may need to be considered for patients with these findings to prevent the potential failure of IET and delayed control of infection.

Model selection is a challenging process of choosing proper machine learning models among many candidates for predicting a specific outcome. In addition to model performance, there are other competing priorities during model selection, such as complexity, maintainability, and explainability (28). Overly simplified or complicated models commonly lead to suboptimal model performance. Therefore, the optimal model should have just enough complexity, and no more. Attempts to develop a model that works in all cases have failed (29). Alas, with each new problem and each new dataset, data scientists must go through the tedious and sometimes laborious process of finding the right-sized model for the analysis of interest. To this end, we compared three different classes of models with three different levels of complexity: *1*) L1-penalized logistic regression, which is relatively low complexity; *2*) nonlinear SVM, which is marginally more complex; and *3*) gradient boosted models, which served as our most complex models in this study. We compared two implementations of gradient boosted models, XGBoost and LightGBM, because these two models differ with respect to their speed of calculation. Because LightGBM builds histograms for all features in the dataset and uses these histograms to find the best split points, it results in a faster training time (18).

Strengths and Limitations

This study has several strengths. Its multicenter design improves the generalizability of the results across different practice settings, and it validates the significance of the identified predictors, which were detected in a smaller single-center study using a similar technique (10). Moreover, our cohort's data collection spanned over a long period of time, allowing for a more comprehensive analysis of the study outcomes. We aimed to collect a broad range of data to analyze and identify the clinical parameters that can predict the failure of IET. The study's external validity is robust because of the high rates of data completeness and the identical collection of datasets across multiple centers, despite a few parameters with missing data. We used MICE to iteratively impute the missing data, which is capable of managing missing data from diverse sources, a notable advantage (15). This is achieved by using a series of regression models to approximate missing values, enabling it to comprehend the correlations between variables, even in cases where missing data exist in multiple variables (30, 31). This study had a few limitations. Although IET failure was defined as the lack of resolution of CPPE/empyema on chest CT or the occurrence of any complication, the decision for surgical intervention was based on local clinical practices, which could have introduced selection bias. However, conducting the study across multiple centers helped mitigate the influence of local practices and ensured broader applicability of the findings. Another limitation was the retrospective design, which may lead to biases inherent in such studies. The results should be validated in prospective studies.

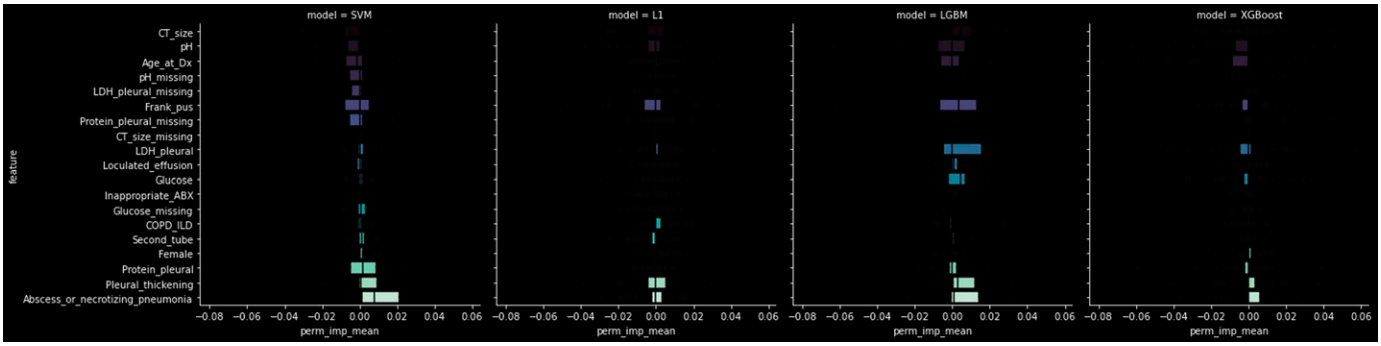

Figure 2. Ranked variable importance from each machine learning model (Note: the most important ranking variables rank from bottom to top). ABX = antibiotics; COPD = chronic obstructive pulmonary disease; CT = computed tomography; Dx = diagnosis; ILD = interstitial lung disease; L1 = L1-penalized logistic regression; LDH = lactate dehydrogenase; LGBM = light gradient-boosting machine; SVM = support vector machine; XGBoost = extreme gradient boosting.

Conclusions

Using four different machine learning models, pleural thickening and the presence of abscess/necrotizing pneumonia are identified as the two most important predictors of IET failure in the setting of pleural space infection. These findings validate a smaller single-center study of similar methodology and may serve as important factors to guide triage of high-risk patients in whom IET is likely to fail and expedite early surgical intervention. Within that context, MIST-3, a multicenter, randomized controlled trial (NCT04161677), is recruiting patients to investigate the feasibility of randomizing patients with pleural infection to early surgery versus early intrapleural tPA/DNase (32). The results of this study may change the management landscape of pleural infection by personalizing proper treatment strategies based on well-defined patient-specific risk factors. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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