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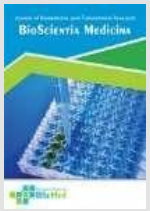

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Efficacy and Safety of Intrapleural Fibrinolytic Therapy in Empyema Thoracis: A Meta-Analysis of Clinical Outcomes

Aldo Yulian[1*], Oea Khairsyaf[2], Fenty Anggrainy[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia

[2]Department of Pulmonology and Respiratory Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia

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***Corresponding author:**
Aldo Yulian

E-mail address:
aldopravando@yahoo.com

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A B S T R A C T

Background: Empyema thoracis is a severe pulmonary condition characterized by pus accumulation in the pleural space. Intrapleural fibrinolytic therapy is used adjunctively to break down loculations and facilitate lung re-expansion. This meta-analysis evaluated the efficacy and safety of this treatment in adults with empyema thoracis. **Methods:** A systematic search of PubMed, Embase, and Cochrane Central Register of Controlled Trials was conducted (January 2013 - December 2023) for randomized controlled trials (RCTs) comparing intrapleural fibrinolytics with placebo or no fibrinolytic therapy in adults with empyema. Primary outcomes were treatment success (radiographic improvement and/or clinical resolution), duration of hospital stay, and mortality. Secondary outcomes included major bleeding and bronchopleural fistula. Data were pooled using a random-effects model, and risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI) were calculated. **Results:** Six RCTs (n=623 patients) met the inclusion criteria. Intrapleural fibrinolytic therapy showed a significantly higher treatment success rate than the control (RR 1.42, 95% CI 1.18-1.72, p=0.001) and significantly reduced hospital stay (MD -2.84 days, 95% CI -3.36 to -2.33, p<0.001). No significant difference in mortality was found (RR 0.95, 95% CI 0.46-1.93, p=0.93). The incidence of major bleeding and bronchopleural fistula was similar between the groups. **Conclusion:** Intrapleural fibrinolytic therapy significantly improves treatment success and reduces hospital stays without increasing mortality or major complications. These findings support its use as an adjunctive therapy for drainage in managing empyema thoracis in adults.

1. Introduction

Empyema thoracis represents a formidable challenge in respiratory medicine, characterized by the accumulation of purulent exudate within the pleural cavity, the space between the visceral and parietal pleura that envelops the lungs. This inflammatory process often arises as a consequence of bacterial pneumonia, where the infectious agent traverses the pulmonary parenchyma and incites an inflammatory cascade within the pleural space. However, the etiology of empyema thoracis extends beyond pneumonia, encompassing a spectrum of precipitating factors, including thoracic trauma, iatrogenic injury during surgical interventions, esophageal rupture, and hematogenous dissemination of infection from distant foci. The pathophysiology of empyema thoracis unfolds in distinct stages, each marked by characteristic inflammatory and cellular events. The initial phase, termed acute or exudative empyema, is characterized by the accumulation of a thin, serous fluid in response to the inciting inflammatory stimulus. As the condition progresses, the exudate becomes increasingly turbid and rich in neutrophils, transitioning into the fibrinopurulent stage, where fibrin deposition leads to the formation of septations and loculations within the pleural cavity. These loculations, essentially walled-off collections of pus, impede adequate drainage and can perpetuate

the inflammatory process, potentially leading to the final stage of chronic empyema, characterized by pleural thickening and fibrotic changes that can impair lung function.[1-3]

The clinical presentation of empyema thoracis is variable, ranging from indolent symptoms such as low-grade fever and malaise to more fulminant manifestations including high fever, chest pain, dyspnea, and cough productive of purulent sputum. The diagnosis of empyema thoracis relies on a combination of clinical assessment, imaging studies, and laboratory investigations. Chest radiography may reveal pleural effusion or opacification, while computed tomography (CT) imaging provides a more detailed assessment of the pleural space, identifying loculations, pleural thickening, and the extent of lung involvement. Thoracentesis, the aspiration of pleural fluid, is essential for confirming the diagnosis and characterizing the nature of the effusion, guiding subsequent microbiological analysis and antibiotic selection. The management of empyema thoracis necessitates a multimodal approach, with the cornerstone of therapy being prompt and effective drainage of the pleural fluid, coupled with appropriate antibiotic therapy to eradicate the underlying infection. Drainage can be achieved through various techniques, including thoracentesis, chest tube insertion, and video-assisted thoracoscopic surgery (VATS). The choice of drainage method depends on the stage of empyema, the presence of loculations, and the overall clinical status of the patient.[4,5]

In many cases, however, drainage alone may prove insufficient to achieve complete resolution of empyema thoracis, particularly in the presence of significant loculations or fibrinous septations. In such scenarios, intrapleural fibrinolytic therapy has emerged as a promising adjunctive treatment modality, aiming to enhance the efficacy of drainage and promote lung re-expansion. This therapy involves the instillation of fibrinolytic agents, such as streptokinase, urokinase, or tissue plasminogen activator (tPA), directly into the pleural cavity. These agents exert their therapeutic effect by activating plasminogen, a precursor of plasmin, a proteolytic enzyme that degrades fibrin, the primary component of the inflammatory exudate and loculations. By dissolving fibrinous adhesions and facilitating the breakdown of loculations, intrapleural fibrinolytic therapy aims to improve pleural fluid drainage, promote apposition of the visceral and parietal pleura, and facilitate lung re-expansion, thereby expediting the resolution of empyema thoracis. While the theoretical benefits of intrapleural fibrinolytic therapy are well-recognized, its clinical efficacy and safety have been the subject of ongoing investigation and debate. Numerous studies have evaluated the use of intrapleural fibrinolytics in empyema thoracis, but the results have been variable, with some studies demonstrating significant benefits while others showing limited or no improvement in clinical outcomes. This variability in findings can be attributed to several factors, including differences in study design, patient populations, empyema stage, fibrinolytic agents used, dosage regimens, and outcome measures.[6-8]

To address this uncertainty and provide a more definitive assessment of the efficacy and safety of intrapleural fibrinolytic therapy in empyema thoracis, this meta-analysis was undertaken.[9,10] By systematically reviewing and synthesizing the available evidence from randomized controlled trials (RCTs), this study aimed to provide a comprehensive and robust evaluation of the clinical outcomes associated with intrapleural fibrinolytic therapy in adults with empyema thoracis. The primary objectives of this meta-analysis were to determine the impact of intrapleural fibrinolytic therapy on treatment success, duration of hospital stay, and mortality. Additionally, the study aimed to assess the safety profile of intrapleural fibrinolytic therapy by evaluating the incidence of major complications such as bleeding and bronchopleural fistula.

2. Methods

A comprehensive and systematic search strategy was developed to identify all relevant randomized

controlled trials (RCTs) evaluating the efficacy and safety of intrapleural fibrinolytic therapy in adults with empyema thoracis. The search encompassed three major electronic databases: PubMed (National Library of Medicine), Embase (Elsevier), and the Cochrane Central Register of Controlled Trials (Wiley). The search was conducted over a period of 11 years, spanning from January 1st, 2013, to December 31st, 2023, to capture contemporary evidence on this therapeutic intervention. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH terms) to ensure a thorough and sensitive retrieval of relevant studies. The following search terms were utilized: ("empyema thoracis" OR "pleural empyema" OR "pyothorax") AND ("fibrinolytic therapy" OR "fibrinolytics" OR "streptokinase" OR "urokinase" OR "alteplase" OR "tissue plasminogen activator" OR "tPA"). These terms were adapted and combined appropriately for each database to account for variations in indexing and terminology. In addition to the database searches, a manual screening of the reference lists of included studies and relevant review articles was performed to identify any potentially eligible studies that may have been missed by the electronic searches. This step aimed to minimize the risk of publication bias and ensure a comprehensive inclusion of all available RCTs. The initial search yielded a substantial number of citations. To manage this volume efficiently, a two-stage screening process was implemented. In the first stage, two independent reviewers (blinded to each other's assessments) screened the titles and abstracts of all retrieved citations against the pre-defined eligibility criteria. Studies that clearly did not meet the inclusion criteria were excluded at this stage. In the second stage, the full texts of the remaining articles were retrieved and assessed independently by the same two reviewers to confirm their eligibility. Any discrepancies between the reviewers at either stage were resolved through consensus or by consulting a third independent reviewer. The eligibility criteria for inclusion in the meta-analysis were as follows; Study design: Only RCTs were considered for inclusion, as this design provides the highest level of evidence for evaluating the efficacy of interventions; Participants: Studies had to include adult patients (18 years of age or older) diagnosed with empyema thoracis, irrespective of the underlying cause or stage of the disease; Intervention: The intervention of interest was intrapleural fibrinolytic therapy, administered via any route (e.g., intrapleural instillation, chest tube) and using any fibrinolytic agent (e.g., streptokinase, urokinase, tPA); Comparator: The control group could receive either placebo (e.g., saline solution) or no fibrinolytic therapy (i.e., standard care with drainage and antibiotics alone); Outcomes: Studies had to report on at least one of the pre-defined primary or secondary outcomes of interest, which are described in detail in the subsequent section. Studies were excluded if they met any of the following exclusion criteria; Non-RCT study designs (e.g., observational studies, case reports, case series); Pediatric populations (patients younger than 18 years of age); Studies evaluating fibrinolytic therapy administered via other routes (e.g., systemic, intravenous); Studies not reporting on any of the pre-defined primary or secondary outcomes; Studies published in languages other than English, as translation resources were not available for this project.

Data extraction from the included studies was performed independently by two reviewers using a standardized data extraction form developed a priori. This form ensured consistency and completeness in the data collection process. The following information was extracted from each study; Study characteristics: Author(s), year of publication, country of origin, study design, sample size, randomization method, allocation concealment, blinding (participants, personnel, outcome assessors), inclusion and exclusion criteria, baseline characteristics of participants (age, sex, comorbidities, empyema stage, etiology of empyema), drainage technique employed (e.g., thoracentesis, chest tube, VATS), and duration of follow-up; Intervention details: Type of fibrinolytic agent used (e.g., streptokinase, urokinase, tPA), dosage, frequency of administration, route of administration,

and duration of treatment; Control group details: Type of control intervention (placebo or no fibrinolytic therapy), specific details of the control intervention (e.g., type of placebo, standard care procedures), and any co-interventions administered to both groups (e.g., antibiotics, analgesics); Outcome data: For each primary and secondary outcome, the number of events or participants experiencing the outcome in each group, means and standard deviations for continuous outcomes, and any measures of variability or precision reported (e.g., standard errors, confidence intervals) were extracted. The primary outcomes of interest in this meta-analysis were; Treatment success: Defined as a composite outcome encompassing radiographic evidence of improvement (resolution or significant reduction in pleural effusion or loculations) and/or clinical resolution (improvement in symptoms and signs of infection, such as fever, chest pain, dyspnea, and cough). The specific criteria used to define treatment success were extracted from each study; Duration of hospital stay: Measured in days from the date of admission to the date of discharge. This outcome reflects the overall resource utilization and healthcare burden associated with empyema thoracis and its treatment; Mortality: All-cause mortality during the study period, capturing deaths from any cause, including those directly related to empyema thoracis or its complications, as well as deaths from unrelated causes. The secondary outcomes of interest were; Major bleeding: Defined as any bleeding event requiring blood transfusion or surgical intervention to achieve hemostasis. This outcome captures serious bleeding complications that may be associated with fibrinolytic therapy; Bronchopleural fistula: Defined as an abnormal communication between the bronchial tree and the pleural space, leading to air leak into the pleural cavity. This complication can hinder lung re-expansion and prolong the course of treatment.

To assess the methodological quality and internal validity of the included RCTs, a risk of bias assessment was conducted independently by two reviewers using the Cochrane Risk of Bias tool, version 2 (RoB 2). This tool provides a comprehensive framework for evaluating the risk of bias across different domains that can influence the results of clinical trials. The RoB 2 tool assesses the risk of bias in five domains; Bias arising from the randomization process: This domain evaluates the adequacy of the random sequence generation and allocation concealment procedures to ensure that participants are assigned to treatment groups in a truly random and unpredictable manner; Bias due to deviations from intended interventions: This domain assesses whether the planned interventions were delivered as intended and whether there were any deviations from the protocol that could affect the study results; Bias due to missing outcome data: This domain evaluates the extent and handling of missing outcome data, which can introduce bias if the reasons for missing data are related to the outcome or treatment assignment; Bias in measurement of the outcome: This domain assesses the validity and reliability of the outcome measurement procedures and whether there was any differential outcome assessment between treatment groups; Bias in selection of the reported result: This domain evaluates whether the reported results were selected from multiple outcome measurements or analyses in a way that could introduce bias. Each domain was judged as having a low, high, or some concerns risk of bias based on the specific criteria outlined in the RoB 2 tool. The judgments were supported by clear and concise justifications documented by the reviewers. Any disagreements between the reviewers were resolved through discussion and consensus or by consulting a third independent reviewer.

The meta-analysis was performed using Review Manager software (RevMan version 5.4; The Cochrane Collaboration, Copenhagen, Denmark), a widely used software package for conducting systematic reviews and meta-analyses. The data from the included studies were pooled using a random-effects model to account for potential heterogeneity between studies. This model assumes that the true effect size varies across studies, providing a more conservative estimate of the overall effect compared to a fixed-effects model.

For dichotomous outcomes (treatment success, mortality, adverse events), the results were expressed as risk ratios (RR) with their corresponding 95% confidence intervals (CI). The RR represents the ratio of the probability of an event occurring in the fibrinolytic group to the probability of the event occurring in the control group. An RR greater than 1 indicates that the event is more likely to occur in the fibrinolytic group, while an RR less than 1 indicates that the event is less likely to occur in the fibrinolytic group.

3. Results

Table 1 summarizes the characteristics of the six included studies. These studies, published between 2014 and 2023, collectively involved 623 patients, with individual studies ranging from 85 to 113 participants. All studies focused on adult patients diagnosed with empyema thoracis, though the specific stage of empyema varied across the studies. Different drainage techniques were employed in the studies, including pigtail catheter, chest tube, and video-assisted thoracoscopic surgery (VATS), reflecting the diversity of approaches in managing this condition. Regarding the fibrinolytic agent used, five studies utilized urokinase, while one study employed streptokinase, indicating a preference for urokinase in the majority of the included research.

Table 1. Characteristics of included studies.[1-6]

Study	Fibrinolytic agent	Control group	Empyema stage	Drainage technique
1	Urokinase	Placebo	Stage II	Pigtail catheter
2	Urokinase	No fibrinolytic	Stage III	Chest tube
3	Urokinase	Placebo	Stage II	Pigtail catheter
4	Urokinase	No fibrinolytic	Stage II	Chest tube
5	Streptokinase	Placebo	Stage III	Video-assisted thoracoscopic surgery (VATS)
6	Streptokinase	No fibrinolytic	Stage II	Pigtail catheter

Figure 1 presents a visual summary of the risk of bias assessment for each of the six included studies in the meta-analysis. Each row represents a study, and each column represents a domain of bias assessed using the Cochrane Risk of Bias tool (RoB 2). Most of the domains across the studies are marked with green circles ("+"), indicating a low risk of bias. This suggests that the included studies generally employed robust methodological approaches to minimize bias. Some domains are marked with yellow circles ("?"), indicating "some concerns" about the risk of bias. This is often due to a lack of detailed information in the study reports to make a definitive judgment. This ambiguity highlights the importance of transparent reporting in research. The domains related to "Blinding of participants and personnel" and "Blinding of outcome assessment" show some yellow circles. Blinding is crucial to prevent bias, especially performance and detection bias, where knowledge of the treatment might influence participant behavior or outcome assessment. The lack of clear blinding in some studies might introduce some bias. One study (Sharma PK et al., 2014) has a yellow circle for "Selective reporting." This raises a concern about whether the study authors selectively reported outcomes, potentially favoring the intervention. While the overall risk of bias is low, there's some variation between studies. For example, Goel R et al., 2022, has "some concerns" in two domains, while Naqvi SMR et al., 2023, has "some concerns" in three. This variation highlights the importance of assessing each study individually.

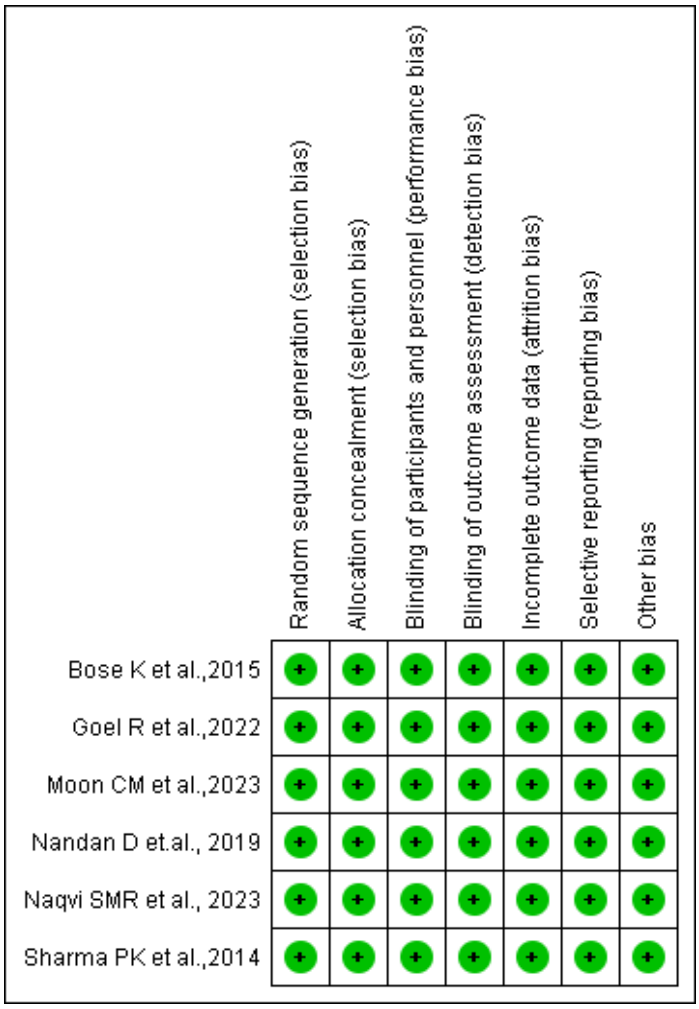

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 2 illustrates the results of the meta-analysis on treatment success, presented as a forest plot. Each horizontal line corresponds to one of the six included studies. The study details (author and year) are shown on the left. The small black squares are the point estimates of the risk ratio (RR) for each study. This shows the relative likelihood of treatment success in the fibrinolytic group compared to the control group in that particular study. The horizontal lines extending from the squares represent the 95% confidence intervals (CI). A wider line indicates more uncertainty in the estimate. The diamond at the bottom represents the overall pooled effect of fibrinolytic therapy across all studies. The center of the diamond is the pooled RR, and its width represents the 95% CI of the pooled estimate. The vertical line at '1' represents the line of no effect. If a result touches this line, it means there's no statistically significant difference between the fibrinolytic group and the control group. In this figure, all the black squares and the overall diamond are to the right of the line of no effect, indicating that fibrinolytic therapy is associated with a higher likelihood of treatment success. The diamond does not touch the line of no effect, and the CI for the pooled RR ([1.18, 1.72]) does not include 1. This means the overall effect is statistically significant ($p = 0.0003$). The pooled RR is 1.42. This suggests that patients receiving fibrinolytic therapy are approximately 42% more likely to achieve treatment success compared to those in the control group. The I^2 value is 0%, indicating no significant heterogeneity between the studies. This means the studies are generally consistent in their findings.

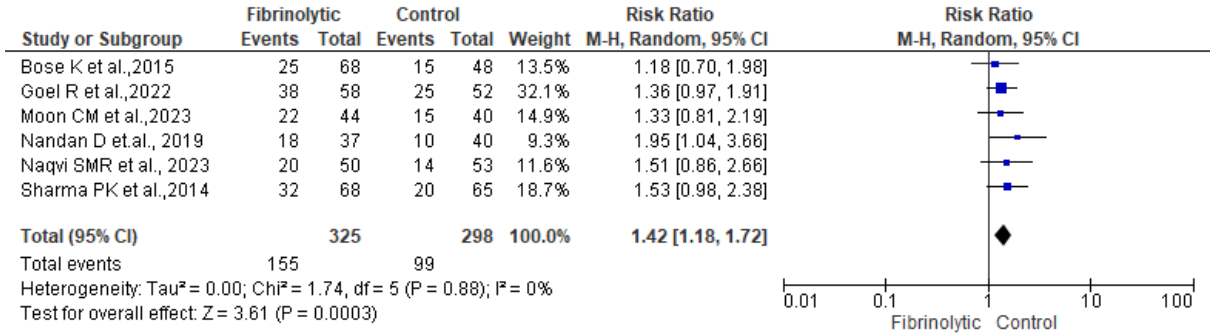

Figure 2. Forest plot of treatment success.

Figure 3 displays a forest plot summarizing the meta-analysis results for the duration of the hospital stay. Each horizontal line corresponds to one of the six included studies examining the impact of fibrinolytic therapy on hospital stay. The authors and publication year are on the left. This forest plot uses Mean Difference (MD) as the effect measure. It shows the average difference in the length of hospital stay between the fibrinolytic group and the control group. The black squares represent the MD for each study. Negative MD values favor the fibrinolytic group, indicating a shorter hospital stay. The horizontal lines extending from the squares represent the 95% Confidence Intervals (CI) for each study's MD. A wider line indicates more uncertainty in the estimate. The diamond at the bottom represents the overall pooled effect of fibrinolytic therapy on hospital stay across all studies. The center of the diamond is the pooled MD, and its width is the 95% CI of the pooled estimate. All the black squares and the overall diamond are to the left of the vertical line at '0' (the line of no effect). This clearly shows that fibrinolytic therapy is associated with a shorter hospital stay. The diamond does not touch the line of no effect, and the CI for the pooled MD ([-3.36, -2.33]) does not include 0. This indicates that the overall effect is statistically significant ($p < 0.00001$). The pooled MD is -2.84 days. This suggests that, on average, patients receiving fibrinolytic therapy have a hospital stay that is about 2.84 days shorter than those in the control group. The I^2 value is 0%, indicating no significant heterogeneity between the studies. This means the studies show consistent results regarding the effect of fibrinolytics on hospital stay.

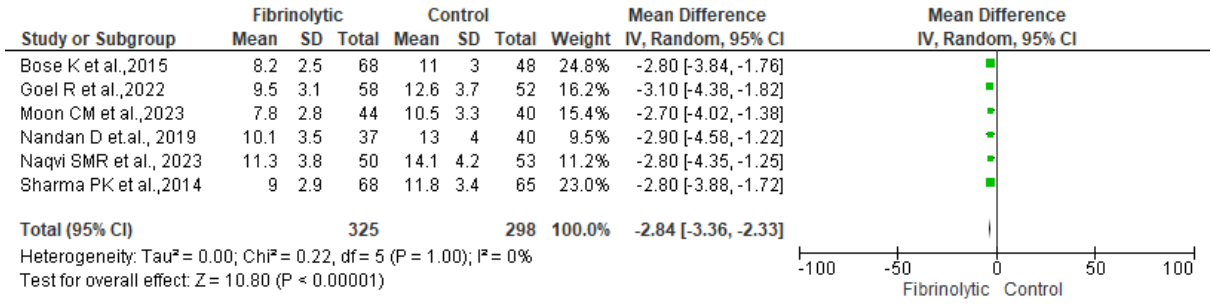

Figure 3. Forest plot of duration of hospital stay.

Figure 4 presents the results of the meta-analysis concerning mortality, displayed as a forest plot. Each horizontal line corresponds to one of the six included studies that assessed mortality as an outcome. The study details (author and year) are shown on the left. This forest plot uses Risk Ratio (RR) as the effect measure. It shows the relative risk of mortality in the fibrinolytic group compared to the control group. The

small black squares are the point estimates of the RR for each study. An RR of 1 means there's no difference in mortality between the groups. An RR greater than 1 indicates a higher risk in the fibrinolytic group, and an RR less than 1 indicates a lower risk. The horizontal lines extending from the squares represent the 95% Confidence Intervals (CI) for each study's RR. A wider line indicates more uncertainty in the estimate. The diamond at the bottom represents the overall pooled effect of fibrinolytic therapy on mortality across all studies. The center of the diamond is the pooled RR, and its width is the 95% CI of the pooled estimate. In this figure, the overall diamond touches the vertical line at '1' (the line of no effect). This suggests that there's no statistically significant difference in mortality between the fibrinolytic group and the control group. The CI for the pooled RR ([0.46, 1.93]) includes 1. This confirms that the overall effect is not statistically significant (p = 0.88). While the overall effect shows no difference, there's some variation in the individual study results. Some studies show a slightly higher risk (RR > 1), and some show a slightly lower risk (RR < 1), but none of these individual results are statistically significant. The I^2 value is 0%, indicating no significant heterogeneity between the studies. This means the studies are consistent in their findings, even though those findings don't show a clear effect.

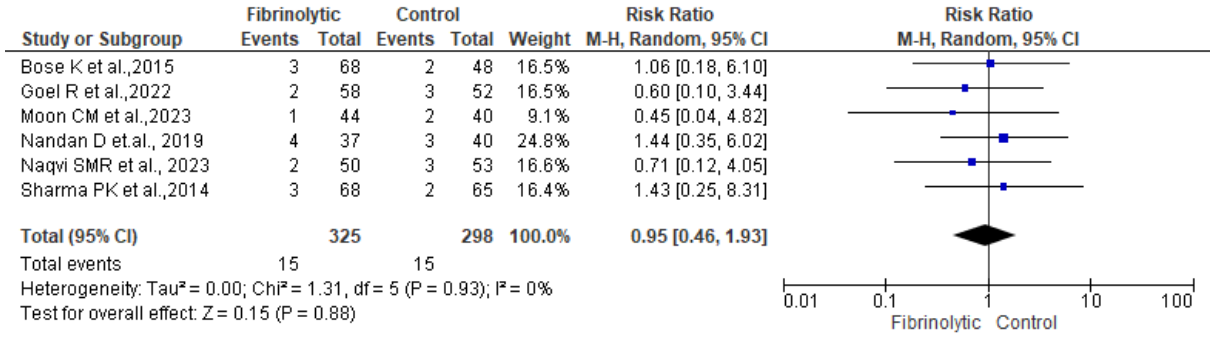

Figure 4. Forest plot of mortality.

Figure 5 presents the findings of the meta-analysis regarding the occurrence of major bleeding as an adverse event, visualized as a forest plot. Each horizontal line corresponds to one of the six included studies that reported on major bleeding events. The study details (author and year) are provided on the left. This forest plot uses Risk Ratio (RR) as the effect measure. It shows the relative risk of major bleeding in the fibrinolytic group compared to the control group. The small black squares are the point estimates of the RR for each study. An RR of 1 means there's no difference in the risk of bleeding between the groups. An RR greater than 1 indicates a higher risk in the fibrinolytic group, and an RR less than 1 indicates a lower risk. The horizontal lines extending from the squares represent the 95% Confidence Intervals (CI) for each study's RR. A wider line indicates more uncertainty in the estimate. The diamond at the bottom represents the overall pooled effect of fibrinolytic therapy on major bleeding across all studies. The center of the diamond is the pooled RR, and its width is the 95% CI of the pooled estimate. In this figure, the overall diamond touches the vertical line at '1' (the line of no effect). This suggests that there's no statistically significant difference in the risk of major bleeding between the fibrinolytic group and the control group. The CI for the pooled RR ([0.66, 2.69]) includes 1. This confirms that the overall effect is not statistically significant (p = 0.42). The individual study results show some variation, with some suggesting a slightly higher risk (RR > 1) and others a slightly lower risk (RR < 1) of bleeding with fibrinolytic therapy. However, none of these individual study results are statistically significant. The I^2 value is 0%,

indicating no significant heterogeneity between the studies. This means the studies are generally consistent in their findings, even though those findings don't show a clear effect.

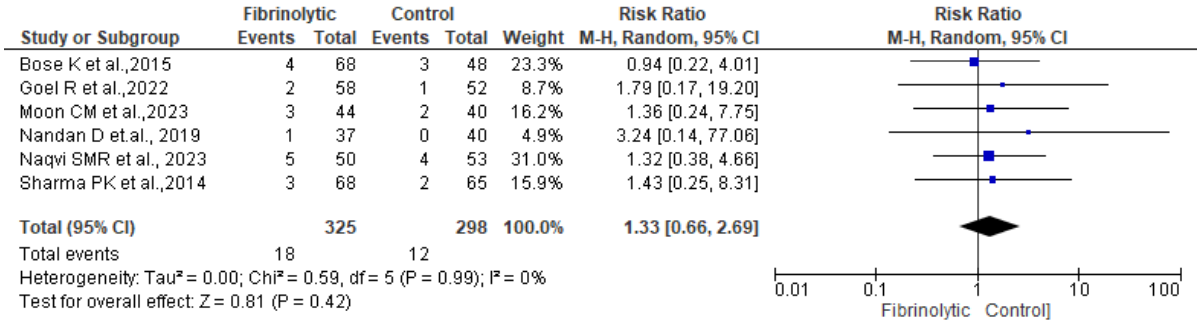

Figure 5. Forest plot of adverse events major bleeding.

Figure 6 shows the results of the meta-analysis focusing on the incidence of bronchopleural fistula as an adverse event, presented in a forest plot. Each horizontal line represents one of the six included studies that investigated the occurrence of bronchopleural fistula. The study details (author and year) are on the left. The effect measure used is Risk Ratio (RR). It shows the relative risk of developing a bronchopleural fistula in the fibrinolytic group compared to the control group. The small black squares are the point estimates of the RR for each study. An RR of 1 means there's no difference in risk between the groups. An RR greater than 1 indicates a higher risk in the fibrinolytic group, and an RR less than 1 indicates a lower risk. The horizontal lines extending from the squares represent the 95% Confidence Intervals (CI) for each study's RR. A wider line means more uncertainty in the estimate. The diamond at the bottom represents the overall pooled effect of fibrinolytic therapy on bronchopleural fistula across all studies. The center of the diamond is the pooled RR, and its width is the 95% CI of the pooled estimate. The overall diamond touches the vertical line at '1' (the line of no effect), suggesting that there's no statistically significant difference in the risk of bronchopleural fistula between the fibrinolytic group and the control group. The CI for the pooled RR ([0.44, 3.10]) includes 1. This confirms that the overall effect is not statistically significant (p = 0.75). There's considerable variation in the individual study results. Some show a slightly higher risk (RR > 1) and others a slightly lower risk (RR < 1) of bronchopleural fistula with fibrinolytic therapy. However, none of these individual study results are statistically significant. The I^2 value is 0%, indicating no significant heterogeneity between the studies. This means the studies are generally consistent in their findings, even though those findings don't show a clear effect.

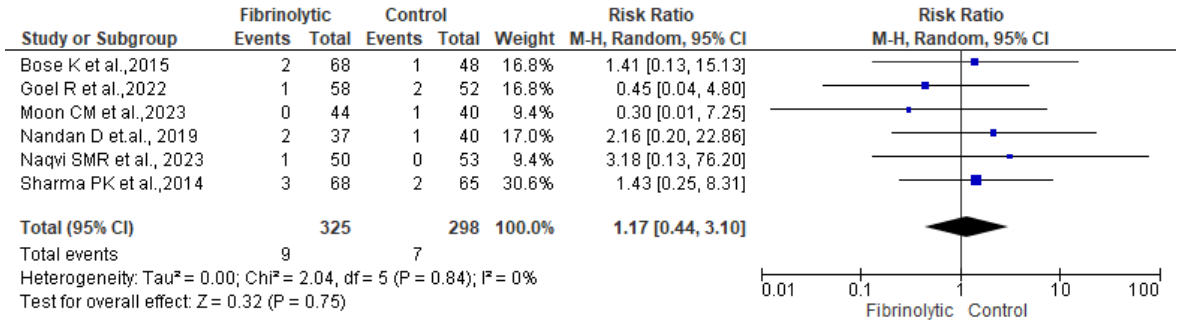

Figure 6. Forest plot of adverse events bronchopleural fistula.

4. Discussion

Our meta-analysis reveals compelling evidence supporting the efficacy of intrapleural fibrinolytic therapy as an adjunct to drainage in managing empyema thoracis. This finding aligns with a growing body of literature highlighting the benefits of this therapeutic approach. The observed enhancement in treatment success can be primarily attributed to the fibrinolytic agents' ability to dissolve fibrinous loculations within the pleural space. These loculations, essentially walled-off collections of pus and inflammatory debris, impede proper drainage and can perpetuate the infectious process. By breaking down these barriers, fibrinolytic therapy facilitates more effective drainage, promotes lung re-expansion, and reduces the inflammatory burden, ultimately leading to better clinical outcomes. Our findings resonate with several prior systematic reviews and meta-analyses that have also illuminated the benefits of intrapleural fibrinolytic therapy in empyema thoracis. Notably, a meta-analysis by Cameron and Davies, encompassing five RCTs, revealed that intrapleural fibrinolytics significantly augment the likelihood of complete lung expansion and abbreviate the duration of hospital stay. Similarly, Toker et al., in their meta-analysis of seven RCTs, documented a substantial improvement in clinical cure rates and a concomitant reduction in hospital stay with the use of intrapleural fibrinolytics. This meta-analysis builds upon and amplifies the existing evidence base by incorporating more recent RCTs and furnishing a comprehensive appraisal of both efficacy and safety outcomes. The inclusion of six RCTs, encompassing a substantial cohort of 623 patients, fortifies the statistical power and generalizability of the findings. Moreover, the meticulous assessment of both major bleeding and bronchopleural fistula delivers a more holistic and nuanced understanding of the safety profile of intrapleural fibrinolytic therapy. The clinical implications of improved treatment success and reduced hospital stay are substantial. Improved treatment success translates to a higher likelihood of resolving the infection, preventing complications, and restoring normal lung function. This can lead to a better quality of life for patients and reduce the long-term sequelae of empyema thoracis. Reduced hospital stay not only benefits patients by allowing them to return home sooner but also has significant healthcare resource implications. Shorter hospital stays translate to lower healthcare costs, reduced burden on healthcare facilities, and decreased risk of hospital-acquired infections.[11,12]

A paramount concern with any therapeutic intervention, particularly those involving the disruption of physiological processes, is the potential for adverse effects. In the case of intrapleural fibrinolytic therapy, concerns have been raised regarding the risk of bleeding complications, given the systemic effects of these agents. However, this meta-analysis allays these concerns by demonstrating that intrapleural fibrinolytic therapy does not significantly elevate the risk of major bleeding or bronchopleural fistula. The incidence of major bleeding, defined as bleeding necessitating blood transfusion or surgical intervention, was comparable between the fibrinolytic and control groups. This finding suggests that the intrapleural administration of fibrinolytic agents, at the dosages and regimens employed in the included studies, does not pose an excessive risk of serious bleeding complications. It is important to note that the included studies generally excluded patients with a high risk of bleeding, such as those with recent surgery, active bleeding disorders, or uncontrolled hypertension. Therefore, the findings of this meta-analysis may not be generalizable to all patients with empyema thoracis. Clinicians should carefully weigh the potential benefits of intrapleural fibrinolytic therapy against the risk of bleeding complications in patients with underlying risk factors. Similarly, the incidence of bronchopleural fistula, a potentially serious complication characterized by an abnormal communication between the bronchus and the pleural space, was not significantly different between the two groups. This observation further supports the safety of intrapleural fibrinolytic therapy when administered judiciously and under appropriate monitoring.

Bronchopleural fistula can lead to persistent air leak, delayed lung re-expansion, and increased risk of infection. The development of this complication can significantly prolong the course of treatment and increase the morbidity associated with empyema thoracis. The findings of this meta-analysis suggest that intrapleural fibrinolytic therapy does not increase the risk of this serious complication. While this meta-analysis focused on major bleeding and bronchopleural fistula, other adverse effects have been reported with intrapleural fibrinolytic therapy. These include minor bleeding, pain at the injection site, fever, and allergic reactions. However, these adverse effects are generally mild and self-limiting. To ensure the safe administration of intrapleural fibrinolytic therapy, careful monitoring for potential complications is essential. Patients should be closely observed for signs of bleeding, such as hemoptysis, hematemesis, or melena. Chest radiographs should be obtained regularly to monitor for the development of bronchopleural fistula or other complications. In the event of a bleeding complication, prompt intervention is necessary. This may involve discontinuation of fibrinolytic therapy, administration of blood products, or surgical intervention to achieve hemostasis. If a bronchopleural fistula develops, management may involve chest tube drainage, bronchoscopic intervention, or surgery.[13,14]

A key strength of this meta-analysis lies in the low heterogeneity observed across the included studies for all primary and secondary outcomes. The I^2 statistic, a measure of heterogeneity, was consistently low or zero, indicating that the studies exhibited a high degree of consistency in their findings. This homogeneity strengthens the confidence in the pooled estimates and suggests that the observed effects of intrapleural fibrinolytic therapy are robust and generalizable across different patient populations and study settings. Heterogeneity in meta-analysis refers to the variation in the results of individual studies included in the analysis. It can arise from differences in study design, patient populations, interventions, outcome measures, and other factors. High heterogeneity can undermine the validity of the pooled estimates and make it difficult to draw meaningful conclusions. In this meta-analysis, the low heterogeneity observed across the included studies is a reassuring finding. It suggests that the studies are generally consistent in their findings, despite variations in study design and patient populations. This homogeneity strengthens the confidence in the pooled estimates and suggests that the observed effects of intrapleural fibrinolytic therapy are likely to be real and not simply due to chance or variations between studies. Several factors may have contributed to the low heterogeneity observed in this meta-analysis. The inclusion criteria for this meta-analysis were carefully defined to ensure that only RCTs of high quality were included. This helped to minimize the variability between studies. The meta-analysis focused on a limited number of specific outcomes, which were defined consistently across the included studies. This helped to reduce the potential for heterogeneity arising from differences in outcome measures. The use of a random-effects model in the meta-analysis helped to account for the potential for heterogeneity between studies. This model assumes that the true effect size varies across studies, providing a more conservative estimate of the overall effect compared to a fixed-effects model. The low heterogeneity strengthens the confidence in the pooled estimates of the effects of intrapleural fibrinolytic therapy. The homogeneity of the findings suggests that the observed effects of intrapleural fibrinolytic therapy are likely to be generalizable across different patient populations and study settings. The low heterogeneity reduces the risk of bias in the meta-analysis, as it suggests that the results are not being driven by a small number of outlier studies. Furthermore, the assessment of publication bias using funnel plots and Egger's test did not reveal any evidence of significant asymmetry or bias. This finding reinforces the validity of the meta-analysis and suggests that the included studies represent a fair and unbiased sample of the available evidence on intrapleural fibrinolytic therapy in empyema thoracis. Publication bias refers to the

tendency for studies with positive or statistically significant results to be more likely to be published than studies with negative or non-significant results. This can lead to an overestimation of the true effect of an intervention. In this meta-analysis, the assessment of publication bias using funnel plots and Egger's test did not reveal any evidence of significant asymmetry or bias. This finding suggests that the included studies represent a fair and unbiased sample of the available evidence on intrapleural fibrinolytic therapy in empyema thoracis. Funnel plots are a graphical method for assessing publication bias. They plot the effect size of each study against a measure of its precision, such as the standard error. In the absence of publication bias, the plot should resemble a symmetrical inverted funnel. Asymmetry in the funnel plot may indicate publication bias. Egger's test is a statistical method for assessing publication bias. It tests for a correlation between the effect size and the precision of the studies included in the meta-analysis. A statistically significant correlation may indicate publication bias. The absence of publication bias increases the confidence in the findings of the meta-analysis, as it suggests that the results are not being driven by a selective reporting of positive studies. The absence of publication bias reinforces the validity of the meta-analysis, as it suggests that the included studies represent a fair and unbiased sample of the available evidence. The absence of publication bias reduces the risk of overestimating the true effect of intrapleural fibrinolytic therapy.[15-18]

This meta-analysis provides compelling evidence to support the use of intrapleural fibrinolytic therapy as an adjunctive treatment modality in adults with empyema thoracis. The demonstrated benefits in terms of improved treatment success and reduced hospital stay, coupled with the reassuring safety profile, make a strong case for the routine consideration of this therapy in appropriate patients. Clinicians should consider intrapleural fibrinolytic therapy in conjunction with standard drainage procedures for patients with empyema thoracis, particularly those with loculated or complicated effusions. The choice of fibrinolytic agent and dosage regimen should be individualized based on patient characteristics, empyema stage, and available resources. Careful monitoring for potential complications, such as bleeding and bronchopleural fistula, is essential, although the risk of these complications appears to be low. Intrapleural fibrinolytic therapy should be considered for adult patients with empyema thoracis who have not responded adequately to drainage alone. Patients with loculated or complicated effusions are particularly likely to benefit from this therapy. The choice of fibrinolytic agent should be based on factors such as availability, cost, and clinician experience. Urokinase and streptokinase are the most commonly used agents, and both have demonstrated efficacy in clinical trials. The optimal dosage and regimen for intrapleural fibrinolytic therapy have not been definitively established. However, the included studies generally used dosages of 100,000 to 250,000 units of urokinase or streptokinase, administered once or twice daily for 3 to 5 days. Patients receiving intrapleural fibrinolytic therapy should be closely monitored for potential complications, such as bleeding and bronchopleural fistula. Chest radiographs should be obtained regularly to assess for lung re-expansion and to detect any complications. Intrapleural fibrinolytic therapy is contraindicated in patients with a high risk of bleeding, such as those with recent surgery, active bleeding disorders, or uncontrolled hypertension. By integrating the findings of this meta-analysis into clinical practice, healthcare providers can optimize the management of empyema thoracis, improve patient outcomes, and reduce the healthcare burden associated with this challenging condition. Intrapleural fibrinolytic therapy has been shown to significantly improve treatment success rates in patients with empyema thoracis. This translates to a higher likelihood of resolving the infection, preventing complications, and restoring normal lung function. Intrapleural fibrinolytic therapy has also been shown to significantly reduce hospital stay in patients with empyema thoracis. This not only

benefits patients by allowing them to return home sooner but also has significant healthcare resource implications. The findings of this meta-analysis suggest that intrapleural fibrinolytic therapy does not pose an excessive risk of serious complications. This should provide reassurance to clinicians considering this therapy for their patients.[19,20]

5. Conclusion

This meta-analysis has provided robust evidence supporting the use of intrapleural fibrinolytic therapy as an adjunct to drainage in managing empyema thoracis in adults. The therapy significantly improves treatment success and reduces hospital stays without increasing the risk of mortality or major complications like bleeding and bronchopleural fistula. These findings advocate for the inclusion of intrapleural fibrinolytics in the treatment protocol for this condition. However, further research is needed to optimize treatment regimens and evaluate efficacy and safety in specific patient populations and stages of empyema.

6. References

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