

Therapeutic Potential of Lumbrokinase in Acute Ischemic Stroke: A Meta-Analysis of Efficacy and Safety

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Background: Acute ischemic stroke (AIS) requires rapid treatment. Although alteplase is a standard thrombolytic therapy, its limited availability in low-resource settings presents a challenge. Lumbrokinase, a fibrinolytic enzyme isolated from earthworms, has been proposed as an adjunct treatment option. This meta-analysis evaluated efficacy and safety in addition to supportive care.

Methods: A systematic review of randomized controlled trials (RCTs) was conducted using multiple databases through July 2024 following PRISMA guidelines. The risk of bias was assessed using RoB 2.0, and evidence quality was graded using GRADE. Publication bias was evaluated using funnel plots. Meta-analyses employed a random-effects model and reported odds ratios (ORs) and mean differences (MDs) with 95% confidence intervals. Primary outcomes included the Barthel Index and NIHSS scores, and secondary outcomes included adverse events and laboratory results.

Results: A total of 35 RCTs published between 2010 and 2024 were included. Compared with supportive care alone, lumbrokinase adjunct therapy significantly improved Barthel Index scores (MD = 15.17; 95% CI: 14.60 to 15.74) and reduced NIHSS scores (MD = -2.01; 95% CI: -2.06 to -1.97). Safety analyses revealed no significant increase in adverse events including gastrointestinal discomfort (OR = 1.00; 95% CI: 0.32 to 3.16) and GI bleeding (OR = 1.42; 95% CI: 0.55 to 3.67). Laboratory assessments indicated improvements in aPTT (MD = 1.93; 95% CI: 1.58 to 2.28), platelet aggregation rate (MD = -205.86; 95% CI, -206.77 to -204.96), and D-dimer levels (MD = -0.04; 95% CI: -0.05 to -0.03).

Conclusion: Lumbrokinase may safely improve stroke outcomes; however, limited evidence warrants cautious use and further high-quality trials.

Keywords: acute ischemic stroke, adjunctive therapy, lumbrokinase, meta-analysis, stroke rehabilitation

Introduction

Acute ischemic stroke is one of the most prevalent diseases in the world, affecting 77 million people worldwide with a mortality rate of 3.3 million each year, becoming the second leading cause of death after heart disease.¹ The disease affected 8.3% of the population, causing a death toll of up to 192 deaths per 100,000 people and costs up to 2.57 trillion rupiahs.² The burden of stroke extends beyond death tolls because it is a leading cause of long-term disability. Around five million of stroke survivors suffer from permanent disabilities, such as vision loss, speech loss, paralysis, confusion, and thus lowers productivity and quality of life.³ These debilitating effects of stroke can be mitigated by early and effective interventions for acute ischemic stroke.⁴

Alteplase is the standard therapy for acute stroke. As a recombinant tissue plasminogen activator (rt-PA), alteplase must be administered within less than 4.5 hours of onset in stroke patients with no contraindications. Delayed treatment with alteplase will only diminish the effects or even worsen, and it will increase the risk of intracranial hemorrhage.⁵ This poses challenges for developing countries with their problems in recognition, admission, and diagnosis of stroke patients. Knowledge regarding stroke symptoms, awareness of the window period, and decision-making continue to contribute to delays.^{6,7} Other than that, inaccessible areas and low-income status have restricted stroke patients from accessing costly thrombolytic agents.⁷ These problems are aggravated by the limited availability of hospitals performing thrombolysis.^{2,8} As the gold standard therapy for acute ischemic stroke, alteplase still has its own limitations, especially when applied in developing countries. Therefore, alternative and adjuvant therapies have been recommended.

Lumbrokinase, a fibrinolytic agent, has been deemed a potential adjuvant therapy for ischemic stroke. This fibrinolytic enzyme, specifically *Lumbricus* sp., has inhibitory effects on platelet aggregation and is currently being rigorously studied for the treatment of various diseases, including cardiovascular and cerebrovascular diseases. It has the ability to hydrolyze both fibrin and fibrinogen which will prevent the formation of blood clots.⁹ Lumbrokinase has qualities superior to other similar fibrinolytic agents, such as urokinase and streptokinase, due to its higher thermal stability, alkali resistance, no conversion of plasminogen into plasmin, and highly specific to fibrin. Due to that, lumbrokinase can be administered orally, can reduce the risk of hemorrhage, and does not induce hyperfibrinolysis.^{10,11} Other than that, due to its natural availability and non-invasive nature, lumbrokinase cuts off unnecessary expenses and does not pose various risks.¹² The overall ability and characteristics of lumbrokinase exhibit valuable potential as a therapeutic agent in treating stroke.

Lumbrokinase is typically administered orally in capsule form, which makes it more practical and non-invasive for stroke patients, particularly in low-resource settings. Studies have also explored intravenous and intramuscular routes, but oral administration remains the most common and accessible approach. Compared to alteplase – and even the newer drug, tenecteplase – lumbrokinase is considered less expensive, particularly in developing countries where healthcare costs are a major barrier to standard thrombolytic therapy. However, robust evidence for lumbrokinase as an adjunctive therapy for ischemic stroke is scarce. This increases the urgency for the systemic evaluation of lumbrokinase to treat ischemic stroke patients, including its efficacy and safety, when compared with standard supportive management. This paper unveils the efficacy and safety of lumbrokinase as an adjunctive therapy combined with supportive management for acute stroke when compared with standard management alone.

Methods

Study Design

A systematic review and meta-analysis was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020.^{13,14}

Data Sources and Search Strategy

A literature search was conducted independently and comprehensively up to July 2024 throughout several databases, including PubMed, Science Direct, EMBASE, EBSCO, Clinical key, Scopus, Proquest, MedRxiv, BioRxiv, SSRN, ClinicalTrials, PsycInfo, PsycNet, Web of Science, Google Scholar, and Cochrane. The keywords that were used are “lumbrokinase”, “acute ischemic stroke”, and “randomized controlled trials”. Any discrepancies were further discussed by the authors. Subsequently, the results were scrutinized for duplication and screened using the predetermined eligibility criteria.

Study Selection

All articles were independently reviewed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. A screening process was started through title and abstract and continued with full-text screening of selected studies to exclude studies that met the exclusion criteria. We included RCTs comparing

lumbrokinase with supportive management to supportive management alone and excluded any other study designs such as non-RCTs and observational studies. All the selected studies were validated to ensure their eligibility for the next step.

Although older and smaller RCTs were included, they were retained based on predefined eligibility criteria and the limited availability of large, high-quality trials evaluating lumbrokinase in acute ischemic stroke. These studies contribute valuable data to a relatively under-researched area, and their inclusion allows for a more comprehensive understanding of the intervention's efficacy and safety.

Outcomes Measured

This study measured both the primary and secondary outcomes to evaluate the effectiveness and safety of the intervention. The primary outcomes included the Barthel Index and NIHSS score, which assess functional independence and neurological deficits, respectively. Secondary outcomes included adverse events, such as gastrointestinal discomfort and bleeding, along with laboratory parameters, such as activated partial thromboplastin time (aPTT) and D-dimer levels.

Data Analysis

To ensure the reliability of the findings, the risk of bias in each included study was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool.^{15,16} Statistical analysis was conducted using a random effects model to account for potential variability among studies. The results were reported as odds ratios (OR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, each with corresponding 95% confidence intervals (CI).

To evaluate publication bias, funnel plots were visually inspected for asymmetry, which may have indicated selective reporting. Heterogeneity among the included studies was assessed using the I^2 statistic, which quantifies the proportion of total variation in the effect estimates owing to heterogeneity rather than chance. An I^2 value of 0% indicated no observed heterogeneity, values above 50% indicated substantial heterogeneity, and values above 75% indicated considerable heterogeneity. The presence of significant heterogeneity may reflect clinical, methodological, or statistical differences between studies, which informs the interpretation of the pooled estimates in the meta-analysis.

Results

A total of 64 studies^{17–80} were included in the analysis as illustrated in the PRISMA flowchart (Figure 1). These studies were selected after a comprehensive screening process that involved the identification of 1836 records through database searches and manual reviews, followed by the exclusion of 1773 duplicates and irrelevant studies. The final dataset comprised randomized controlled trials evaluating the efficacy and safety of the intervention across various clinical and laboratory outcomes, which are summarized in Table 1. The risk of bias is shown in Figure 2.

Adverse events were grouped into five groups; three studies^{60,69,79} reported GI discomfort, and the results shown in Figure 3 showed that there was no significant difference between the experimental and control groups, with an OR of 1.00 [95% CI 0.32; 3.16]. Seven studies^{36,38,47,56,58,69,79} reported vomiting, and the results shown in Supplementary Figure 1 showed that the experimental group was favorable with an OR of 2.00 [95% CI 0.74; 5.39], rash with an OR of 1.64 [95% CI 0.38; 7.01],^{47,56,69} and GI tract bleeding with an OR of 1.42 [95% CI 0.55; 3.67].^{19,65,79} Heterogeneity was absent across groups, and the funnel plot showed no evidence of heterogeneity.

Eight studies^{26,38,57,66,69,73,77,80} reported aPTT, and the results as seen in Supplementary Figure 2 showed that the control group is favorable with MD of 1.93 [95% CI 1.58; 2.28]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Nine studies^{19,27,38,51,63,64,69,79,80} reported the Barthel Index, and the results as seen in Supplementary Figure 3 showed that the control group is favorable with MD of 15.17 [95% CI 14.60; 15.74]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Three studies^{20,75,77} reported carotid artery intima media thickness, and the results as seen in Supplementary Figure 4 showed that the experimental group is favorable with MD of -0.27 [95% CI -0.36; -0.17]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity.

Four studies^{47,48,53,63} reported cell aggregation rate, and the results as seen in Supplementary Figure 5 showed that the control group is favorable with MD of 0.31 [95% CI 0.26; 0.36]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Two studies^{54,55} reported coagulation factor, and the results as seen in

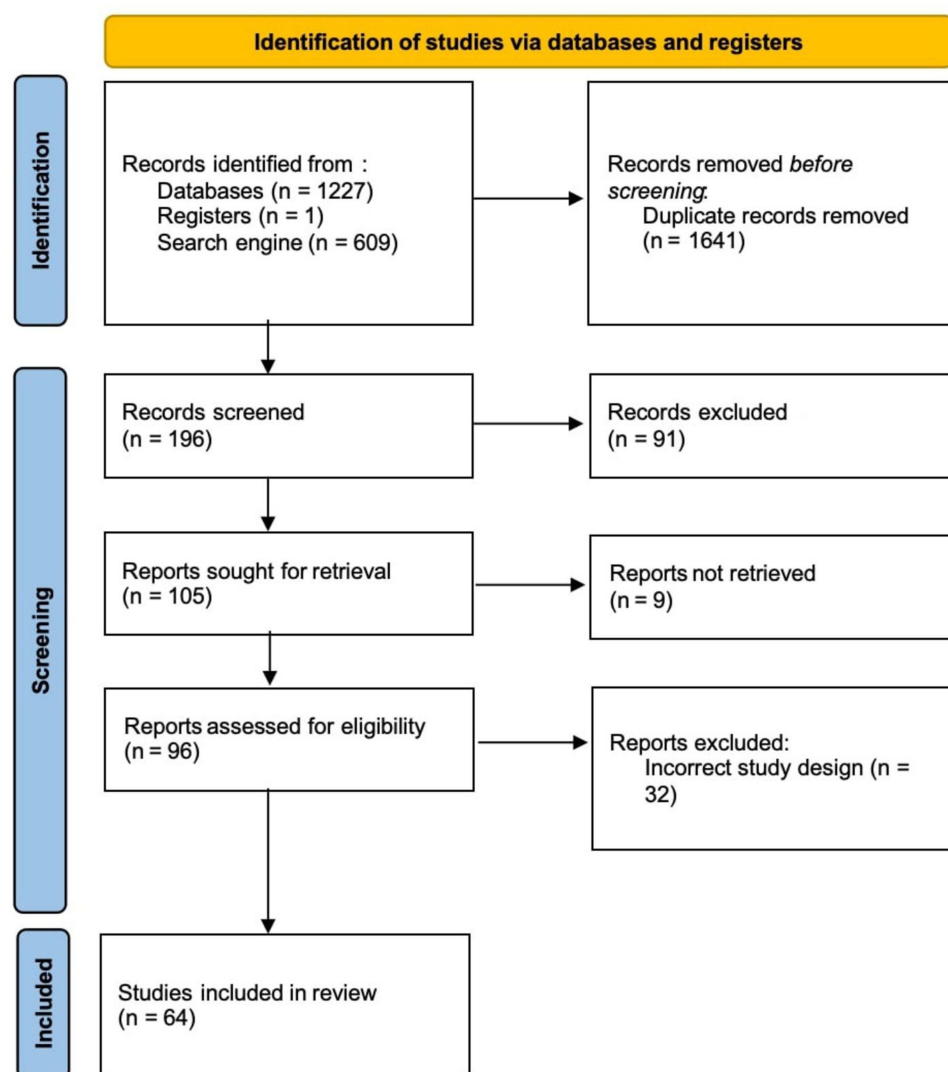


Figure 1 PRISMA 2020 flowchart of the included studies.

[Supplementary Figure 6](#) showed that the experimental group is favorable with MD of -0.62 [95% CI -0.88 ; -0.35]. Heterogeneity was low, and the funnel plot showed no evidence of true heterogeneity. Five studies^{17,18,21,65,77} reported CRP, and the results as seen in [Supplementary Figure 7](#) showed that the experimental group is favorable with MD of -1.40 [95% CI -1.47 ; -1.34]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Thirty five^{19,33–42,44–46,48,51,52,54–62,64–66,69–74} studies reported curative effect, and the results as seen in [Supplementary Figure 8](#) showed that experimental group is favorable with odds ratio of 2.77 [95% CI 2.33 ; 3.29]. Heterogeneity was moderate, and the funnel plot showed few outliers, indicating true heterogeneity.

Six studies^{38,66,69,74,77,78} reported D-dimer, and the results shown in [Supplementary Figure 9](#) showed that the experimental group was favorable, with an MD of -0.04 [95% CI -0.05 ; -0.03]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Three studies^{48,55,62} reported erythrocyte sedimentation rate, and the results as seen in [Supplementary Figure 10](#) showed that the experimental group is favorable with MD of -0.58 [95% CI -2.55 ; -1.40]. Heterogeneity was low, and the funnel plot showed no evidence of true heterogeneity.

Eight studies^{33,36,43,51,54,55,62,73} reported hematocrit, and the results as seen in [Supplementary Figure 11](#) showed that the control group is favorable with MD of 0.07 [95% CI 0.06 ; 0.08]. Heterogeneity was high, and the funnel plot showed

Table 1 Summary of Key Outcomes from the Meta-Analysis on Lumbrokinase's Effectiveness and Safety in Treating Acute Ischemic Stroke

Outcome Measure	Number of Studies	MD	95% CI	p-value	I ²
aPTT	8	1.93	1.58 to 2.28	< 0.00001	93%
Barthel Index	9	15.17	14.60 to 15.74	< 0.00001	97%
Carotid Artery Intima Media Thickness	3	-0.27	-0.36 to -0.17	< 0.00001	95%
Cell Aggregation Rate	4	0.31	0.26 to 0.36	< 0.00001	98%
Coagulation Factor	2	-0.62	-0.88 to -0.35	< 0.00001	0%
CRP	2	-1.40	-1.47 to -1.34	< 0.00001	99%
Curative Effect	35	2.77	2.33 to 3.29	< 0.00001	69%
D-dimer	6	-0.04	-0.05 to -0.03	< 0.00001	99%
Erythrocyte Sedimentation Rate	3	-0.58	-2.55 to -1.40	0.57	0%
Hematocrit	8	0.07	0.06 to 0.08	< 0.00001	99%
INR	3	0.05	0.02 to 0.09	0.004	0%
MRS Score	3	-1.28	-1.54 to -1.05	< 0.00001	99%
NIHSS Score	26	-2.01	-2.06 to -1.97	< 0.00001	94%
Number of Carotid Plaques (Blocks)	3	-0.00	-0.13 to 0.12	0.94	0%
Plasma Fibrinogen	33	-1.00	-1.03 to -0.96	< 0.00001	98%
Plasma Specific Viscosity	22	-0.16	-0.17 to -0.14	< 0.00001	96%
Plasminogen Activator Inhibitor	5	-0.77	-0.85 to -0.69	< 0.00001	96%
Platelet Aggregation Rate (0.5 Minute)	3	-205.86	-206.77 to -204.96	< 0.00001	100%
Platelet Aggregation Rate (1 Minute)	9	-7.25	-8.61 to -5.90	< 0.00001	86%
Platelet Aggregation Rate	2	6.59	3.22 to 9.96	0.0001	98%
Platelet Count	7	-8.78	-13.49 to -4.07	0.0003	64%
PT (Second)	17	-0.17	-0.22 to 0.12	< 0.00001	98%
RBC Deformation Coefficient	3	-0.33	-0.39 to -0.27	< 0.00001	42%
Thrombosis Precursor Protein	2	-3.10	-3.99 to -2.21	< 0.00001	0%
Tissue Plasminogen Activator	4	0.22	0.19 to 0.24	< 0.00001	99%
Total Cholesterol	2	-0.92	-1.20 to -0.65	< 0.00001	98%
Triacylglycerol	2	-0.46	-0.66 to -0.25	< 0.0001	27%
TT (Second)	2	-0.08	-0.48 to 0.32	0.69	0%
Whole Blood High Viscosity Shear	17	-0.14	-0.16 to -0.12	< 0.00001	99%
Whole Blood Low Viscosity Shear	15	-1.29	-1.40 to -1.17	< 0.00001	88%
Whole Blood Reduced Viscosity	6	0.03	0.01 to 0.05	0.003	96%
Whole Blood Specific Viscosity	5	-0.67	-0.78 to -0.57	< 0.00001	76%
Whole Blood Viscosity Mid-Cut	4	-0.42	-0.53 to -0.30	< 0.00001	93%
Outcome Measure	Number of Studies	OR	95% CI	p-value	I ²
Adverse Event					
GI Discomfort	3	1.00	0.32 to 3.16	0.76	0%
Vomiting	7	2.00	0.74 to 5.39		
Rash	3	1.64	0.38 to 7.01		
Skin Bleeding	1	0.26	0.01 to 6.76		
GI Tract Bleeding	3	1.42	0.55 to 3.67		
Clinical Efficacy					
Cured	7	1.12	0.83 to 1.52	< 0.0001	79%
Markedly Effective / Effective	5	0.92	0.62 to 1.38		
Efficient	5	1.12	0.72 to 1.76		
Ineffective	5	0.26	0.15 to 0.47		
Always Effective	3	1.18	0.67 to 2.10		
Deterioration	2	0.38	0.13 to 1.12		
Total Effectiveness	4	1.38	0.81 to 2.35		
Basic Progress + Significant Progress	2	2.20	1.21 to 4.01		

Abbreviations: MD, mean difference; CI, confidence interval; aPTT, activated partial thromboplastin time; CRP, C-reactive protein; INR, international normalized ratio; MRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; RBC, red blood cell; TT, thrombin time; OR, odds ratio; GI, gastrointestinal.

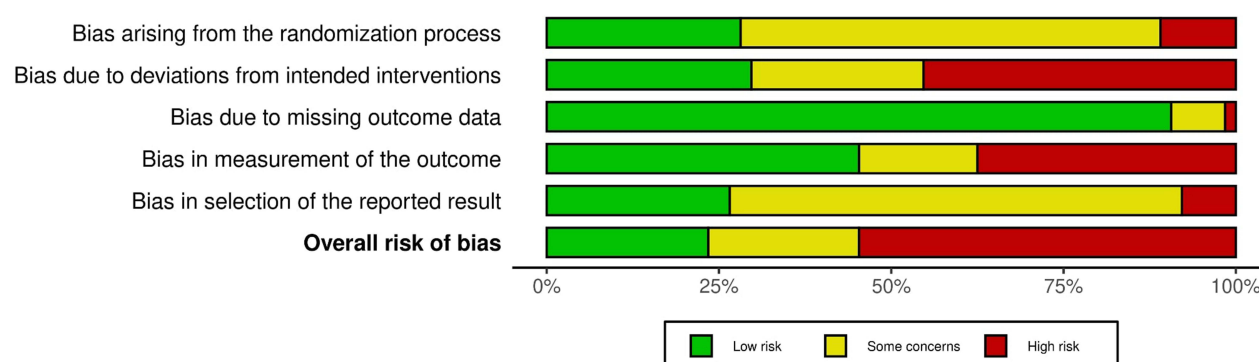


Figure 2 Risk of bias of the included studies.

few outliers, indicating evidence of true heterogeneity. Three studies^{19,77,80} reported INR, and the results as seen in [Supplementary Figure 12](#) showed that the control group is favorable with MD of 0.05 [95% CI 0.02; 0.09]. Heterogeneity was low, and the funnel plot showed no evidence of true heterogeneity. Three studies^{65,66,79} reported mRS score, and the results as seen in [Supplementary Figure 13](#) showed that the experimental group is favorable with MD of -1.28 [95% CI -1.54; -1.05]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity.

Twenty four studies^{19,25,28,32,37,38,42,47,48,50,55,56,59,60,64–69,71,76–79} reported NIHSS Score, and the results as seen in [Supplementary Figure 14](#) showed that the experimental group is favorable with MD of -2.01 [95% CI -2.06; -1.97]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Two studies^{20,77} reported the number of carotid plaques, and the results shown in [Supplementary Figure 15](#) showed that there was no difference between the experimental and control groups (MD -0.00 [95% CI -0.13; 0.12]). Heterogeneity was low, and the funnel plot showed no evidence of true heterogeneity. Thirty three^{18–21,25,36,37,39,40,43,45,47–50,52,53,56,57,59,62,63,66–69,71–74,76,77} studies reported plasma fibrinogen, and the results as seen in [Supplementary Figure 16](#) showed that the experimental group is favorable with MD of -1.00 [95% CI -1.03; -0.96]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Twenty two studies^{29,33,35,36,39,40,45,47,48,51–55,57,59,62,63,66,68,73,77} reported plasma specific viscosity, and the results as seen in [Supplementary Figure 17](#) showed that the experimental group is favorable with MD of -0.16 [95% CI -0.17; -0.14]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity.

Five studies^{27,38,66,77,78} reported plasminogen activator inhibitor, and the results as seen in [Supplementary Figure 18](#) showed that the experimental group is favorable with MD of -0.77 [95% CI -0.85; -0.69]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Three studies^{53,54,62} reported platelet aggregation rate (0.5 min), and the results as seen in [Supplementary Figure 19](#) showed that the experimental group is favorable with MD of -205.86 [95% CI -206.77; -204.96]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity. Nine studies^{36,38,42,53,63,66,67,73,74} reported platelet aggregation rate (1 min), and the results as seen in [Supplementary Figure 20](#) showed that the experimental group is favorable with MD of -7.25 [95% CI -8.61; -5.90]. Heterogeneity was high, and the funnel plot showed few outliers, indicating evidence of true heterogeneity.

Two studies^{18,72} reported platelet aggregation rate, and the results as seen in [Supplementary Figure 21](#) showed that the control group is favorable with MD of 6.59 [95% CI 3.22; 9.96]. Heterogeneity was high, and the funnel plot indicated evidence of true heterogeneity. Seven studies^{19,26,28,35,37,43,71} reported platelet count, and the results as seen in [Supplementary Figure 22](#) showed that the experimental group is favorable with MD of -8.78 [95% CI -13.49; -4.07]. The heterogeneity was moderate, and the funnel plot indicated evidence of true heterogeneity. Seventeen studies^{21,26,28,31,35,38–40,57,63,66,69,71,77,80} reported PT (second), and the results as seen in [Supplementary Figure 23](#) showed that the experimental group is favorable with MD of -0.17 [95% CI -0.22; 0.12]. Heterogeneity was high, and the funnel plot indicated evidence of true heterogeneity.

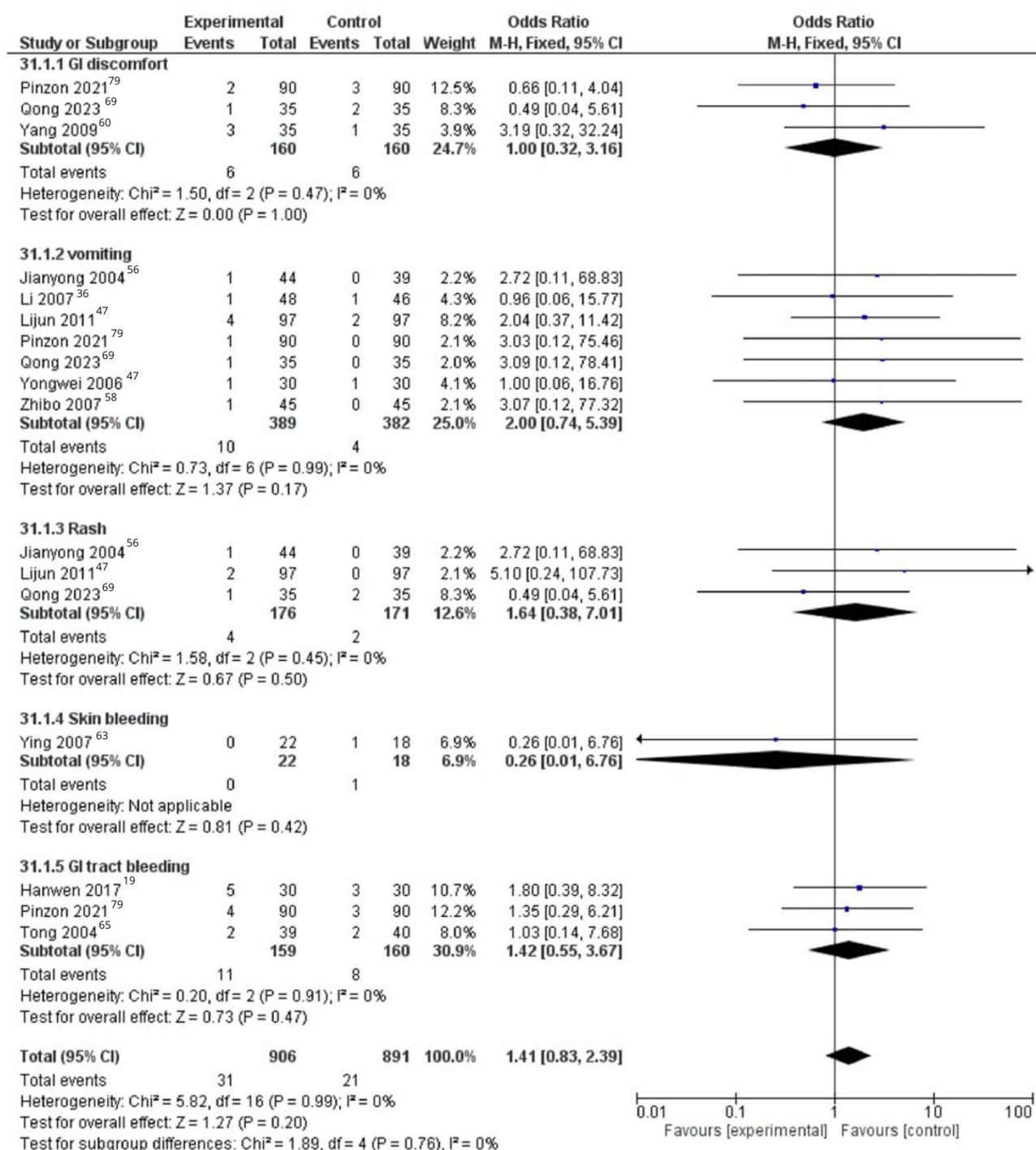


Figure 3 Forest plot of adverse events.

Three studies^{47,55,62} reported red blood cell deformation coefficient, and the results as seen in [Supplementary Figure 24](#) showed that the experimental group is favorable with MD of -0.33 [95% CI -0.39; -0.27]. Heterogeneity was low, and the funnel plot showed no evidence of true heterogeneity. Two studies^{18,21} reported thrombosis precursor protein, and the results as seen in [Supplementary Figure 25](#) showed that the experimental group is favorable with MD of -3.10 [95% CI -3.99; -2.21]. Heterogeneity was absent, and the funnel plot showed no evidence of true heterogeneity. Four studies^{26,38,66,77} reported tissue plasminogen activator, and the results shown in [Supplementary Figure 26](#) showed

that the control group was favorable (MD 0.22 [95% CI 0.19; 0.24]). The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity.

Two studies^{20,54} reported total cholesterol, and the results as seen in [Supplementary Figure 27](#) showed that the experimental group is favorable with MD of -0.92 [95% CI -1.20; -0.65]. The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity. Two studies^{20,54} reported triacylglycerol, and the results as seen in [Supplementary Figure 28](#) showed that the experimental group is favorable with MD of -0.46 [95% CI -0.66; -0.25]. Heterogeneity was low, and the funnel plot showed no evidence of true heterogeneity. Two studies^{38,66} reported TT (second), and the results shown in [Supplementary Figure 29](#) showed that the experimental group was favorable, with an MD of -0.08 [95% CI -0.48; 0.32]. Heterogeneity was absent, and the funnel plot showed no evidence of true heterogeneity.

Seventeen studies^{23,29,33,35,36,38,48,51-55,57,59,69,73,77} reported whole blood high viscosity shear, and the results as seen in [Supplementary Figure 30](#) showed that the experimental group is favorable with MD of -0.14 [95% CI -0.16; -0.12]. The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity. Fifteen studies^{23,29,33,35,36,48,52-55,57,59,69,73,77} reported whole blood low viscosity shear, and the results as seen in [Supplementary Figure 31](#) showed that the experimental group is favorable with MD of -1.29 [95% CI -1.40; -1.17]. The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity. Six studies^{48,52,55,62,66,68} reported whole blood reduced viscosity, and the results as seen in [Supplementary Figure 32](#) showed that the control group is favorable with MD of 0.03 [95% CI 0.01; 0.05]. The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity. Five studies^{18,21,28,66,68} reported whole blood specific viscosity, and the results as seen in [Supplementary Figure 33](#) showed that the experimental group is favorable with MD of -0.67 [95% CI -0.78; -0.57]. The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity. Four studies^{36,38,53,77} reported whole blood viscosity mid-cut, and the results as seen in [Supplementary Figure 34](#) showed that the experimental group is favorable with MD of -0.42 [95% CI -0.53; -0.30]. The heterogeneity was high, and the funnel plot showed evidence of true heterogeneity.

Clinical efficacy was divided into seven groups, as shown in [Supplementary Figure 35](#), and eight groups showed that the results favored the experimental group. Heterogeneity was high across the groups, and the funnel plot showed true evidence of heterogeneity.

Discussion

Lumbrokinase has been known to have anti-ischemic properties through inhibition of platelet aggregation and promotion of platelet disintegration.⁸¹ Based on the result of this meta-analysis, it is shown that lumbrokinase can improve functional outcomes in acute ischemic stroke patients compared to those with standard therapy. These were concluded by significant improvements in the functional outcome components, such as improvements in the Barthel Index and lowered NIHSS and mRS scores. These results suggest a positive efficacy of lumbrokinase in the treatment of acute ischemic stroke.

In addition to its fibrinolytic properties, lumbrokinase can lower stress in the endoplasmic reticulum. This meta-analysis found improvements in the Barthel Index in the lumbrokinase group compared to that in the control group, suggesting higher independence in the lumbrokinase group. The Barthel Index, which is commonly used to observe improvements during or after rehabilitation, can depict a patient's dependency in daily life. A study in mice showed that stroke-induced endoplasmic reticulum stress was reduced by decreasing the phosphorylation of inositol-requiring enzyme-1 (IRE1) and attenuating autophagy and inflammation. Lower IRE1 levels are associated with lower activity of apoptosis-promoting pathways.⁸² Our study is in agreement with previous studies. Thus, lumbrokinase exhibits neuroprotective functions, prevents neuronal death, and further halts the worsening of Barthel Index score. Therefore, it can be inferred that lumbrokinase can increase independence in daily life in patients with acute ischemic stroke compared to those treated with standard therapy. In addition, the NIHSS and mRS scores, which reflect neurological deficits, were lower in the lumbrokinase group. Despite its clear effect favoring the lumbrokinase group, we also found high heterogeneity, which indicated variability in the study results. Differences in the study design, follow-up duration, and baseline data could potentially affect the results. More studies are needed to explore the neuroprotective and neurorehabilitative effects of lumbrokinase in patients with acute stroke.

Current standard therapies for acute ischemic stroke, such as antiplatelet and thrombolytic agents, have shown significant clinical benefits in daily usage. However, adverse effects such as an increased risk of bleeding complications remain a major clinical concern. Alternatives with similar efficacies have been rigorously investigated to minimize complications. In this meta-analysis, we found that there was no significant increase in adverse events in the lumbrokinase group compared with the control group. This suggests that despite its high fibrinolytic activity, lumbrokinase does not cause a higher adverse effect than the standard therapy. Previous studies have shown that the fibrinolytic properties of lumbrokinase are highly specific for fibrin; plasminogens are not activated into plasmin with lumbrokinase. Therefore, they are only active in the presence of fibrin.⁸³ Meanwhile, other thrombolytics, such as tPA, are not specific for fibrin. Thus, adverse effects, especially bleeding effects, are minimized in the lumbrokinase group by this mechanism.⁸⁴ We also did not find any significant differences in other adverse effects, such as gastrointestinal discomfort, vomiting, and rash between lumbrokinase therapy and standard therapy.

Various laboratory test results were compared between the two groups. One such test is aPTT, which reflects the ability of platelets to form blood clots and stop bleeding. Our study found that aPTT was significantly longer in the lumbrokinase group. Lower platelet aggregation rates, whether at 0.5 second or 1 second, were observed in the lumbrokinase group. Moreover, D-dimer levels were lower in the kinase group. This supports previous studies that stated its antithrombotic potential.⁸¹ Whilst laboratory results might have statistically significant differences between groups, several precautions should be accounted for. A previous study stated that only aPTT is likely to develop moderate to severe bleeding.⁸⁵ Our study shows that the mean time for aPTT lies between 22 and 39.9 seconds in the lumbrokinase group, while in the standard therapy group it ranged from 24 to 37.72 seconds. Another study also found that shortened aPTT, defined as shorter than 28.4 seconds, is an independent factor for ischemic stroke, stroke severity, and neurological decline.⁸⁶ Previous study conducted by Nurindar et al found that there was only a weak positive correlation between lower platelet aggregation rate and the degree of neurological deficit, and no statistically significant result was observed in the study.⁸⁷ A study conducted by Zi et al found that the range of D-dimer in acute ischemic stroke was 0.28 to 2.11 mg/L,⁸⁸ while our study reports a range from 0.007 to 0.91 mg/L in the lumbrokinase group and 0.07 to 0.65 mg/L in the control group. Thus, even when lumbrokinase is found to statistically improve laboratory findings, it should not be interpreted alone, and the clinical context should be considered. Although statistically significant, the three indicators also had high heterogeneity, which might be affected by different baseline characteristics, differences in measurement techniques, and study designs.

As previously described, we can infer that lumbrokinase holds potential as an adjuvant or alternative therapy for acute ischemic stroke compared to the standard therapy currently available, especially when resources are limited and access to alteplase might be minimal. Lumbrokinase was isolated and extracted from the earthworm, *Lumbricus rubellus*. These earthworms can be found in several places with limited resources.⁸⁹ have favorable outcomes in improving neurological status and laboratory findings, while having no statistical difference in adverse effects when compared to standard therapy demonstrated its potential. However, the clinical findings should be considered when implementing these findings. Our findings should not be overstated because of our moderate quality of evidence, and alteplase remains the gold-standard therapy based on international guidelines. Further robust research for lumbrokinase in treating acute ischemic stroke with less heterogeneity should be conducted, for our findings of high heterogeneity remain our limitations. We also found that there was a lack of direct comparison between lumbrokinase and alteplase and the moderate-to-high risk of bias studies used in our study, which might have affected our study.

Several limitations must be acknowledged. First, although a large number of RCTs were included, many of them presented a moderate to high risk of bias, which may impact the reliability of pooled estimates. Second, the lack of direct comparisons between lumbrokinase and alteplase limits our ability to determine its effectiveness relative to standard thrombolytic therapy. Third, heterogeneity in study designs, follow-up durations, and baseline characteristics was substantial in several outcomes. Finally, as most included studies were conducted in specific regions, external validity and generalizability remain limited. Future high-quality, multicenter studies are needed to address these concerns.

The findings of this study have notable implications for clinical practice, particularly in low- and middle-income countries where access to intravenous thrombolytics is limited. Lumbrokinase, as an orally administered agent with a favorable safety profile, presents a promising adjunctive or alternative therapy. Its affordability, non-invasive

administration, and comparable efficacy in improving outcomes could help expand stroke care beyond major urban centers. However, clinicians must still interpret laboratory improvements cautiously and consider patient-level characteristics, comorbidities, and timing of therapy.

Lumbrokinase has the potential to improve outcomes and reduce stroke severity, particularly when used in combination with standard supportive care. Further high-quality RCTs with direct comparisons to alteplase, exploration of long-term outcomes, and broader safety profiles may be beneficial for further validation of lumbrokinase use. Although lumbrokinase shows promise in improving outcomes in acute ischemic stroke when combined with supportive management, the results must be interpreted with caution due to low-to-moderate evidence quality, and it should not be considered as a replacement for established thrombolytic agents, such as alteplase, but rather as a [supplementary treatment](#).

Conclusion

Lumbrokinase, a fibrinolytic enzyme derived from earthworms, appears to improve neurological function and reduce laboratory markers of thrombosis in patients with acute ischemic stroke when used alongside supportive care. It offers a safe and potentially cost-effective alternative in settings with limited access to conventional thrombolytic agents. However, high heterogeneity, risk of bias, and lack of direct comparisons with current standard therapies limit definitive conclusions. Future research should focus on large-scale randomized trials comparing lumbrokinase directly with established treatments and evaluating its long-term safety and clinical benefits.

Data Sharing Statement

All data generated or analyzed during the study are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest in this work.

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