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D-Dimer Levels as a Predictor of Clinical Outcome and Mortality in Acute Ischemic Stroke Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: In ischemic stroke, high D-dimer levels are frequently found, indicating coagulation with ongoing thrombus formation and fibrinolysis. **Objective:** The purpose of this study was to analyze the role of D-dimer in predicting clinical outcomes and mortality in acute ischemic stroke patients. **Methods:** A systematic literature search was conducted using the PRISMA method through the PubMed, Science Direct, and Google Scholar databases. The quality of the article was assessed using the Newcastle-Ottawa Scale (NOS) and statistically analyzed using Review Manager software version 5.4.1. **Results**: Eight articles had good quality according to NOS and matched the criteria for the literature search. Elevated D-dimer levels and worsened clinical outcomes have a significant result when discharged from the hospital: OR 2.37 (95% CI 1.68–3.35); I^2 = 45% p < 0.00001; 1-month: OR 1.75 (95% CI 1.38–2.23), I^2 = 47% p < 0.00001; 3-months: OR 2.43 (95% CI 2.00–2.95), I^2 0% p < 0.00001; 6-months: OR 2.64 (95% CI 1.92–3.63), I^2 = 0% p < 0.00001; and 12-months: OR 1.92 (95% CI 1.31–2.82), I^2 = 62% p < 0.0008. Elevated D-dimer level and increased mortality have a significant result with OR 2.25 (95% CI 1.78–2.85), I^2 = 45% p < 0.00001. **Conclusion:** D-dimer can be used as a predictor of clinical outcome and mortality in acute ischemic stroke.

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INTRODUCTION

Stroke is still the leading cause of mortality worldwide and a major cause of disability or complex chronic illness. Ischemic stroke is defined as cell death in the brain, spinal cord, or retina, and focal ischemic injury lasting more than 24 hours based on pathological, radiological, or other objective evidence.[1]

The World Health Organization (WHO) estimates that 7.75 million people worldwide died from strokes in 2018. In 2020, the Centers for Disease Control and Prevention (CDC) estimated that one stroke-related death occurred every four minutes in the United States. Stroke prevalence has increased annually in Indonesia, ranking third after heart disease and cancer. The incidence of stroke increased from 7 per million in 2013 to 10.9 per million in 2018, according to the 2018 RISKESDAS survey. In Indonesia, ischemic stroke accounts for 67% of all strokes.[1,2]

Increased D-dimer levels are present in most patients with acute thrombosis, including acute ischemic stroke, pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation, and venous thromboembolism. Additionally, D-dimer levels are increased in cancer, pregnancy, advanced age, after surgery, chronic inflammation, infection conditions, liver diseases, and renal diseases.[3]

Atherosclerosis, which is characterized by the accumulation of plaque in the intima of arterial blood vessels, is the main etiology for blockage in ischemic stroke. D-dimer is the end product of cross-linked fibrin degradation by the proteolytic activity of plasmin in the fibrinolysis system. Plasmin will dissolve cross-linked fibrin and produce fibrin degradation products (FDPs) and D-dimer as end products. An increase in the D-dimer level indicates coagulation activity with ongoing thrombus formation and fibrinolysis.[3,4,5]

High D-dimer levels are associated with a high risk of poor clinical or functional outcomes, mortality, infarct volume, and worsening of ischemic stroke. D-dimer has a long half-life and can be easily and inexpensively tested using standard laboratory equipment.[5]

The predictor of clinical outcomes can be used as a guide for patient management and for providing more accurate education to patients or their families about their illness. Based on this background, the authors are interested in conducting a systematic review and meta-analysis to analyze D-dimer levels as a predictor of clinical outcomes and mortality in patients with acute ischemic stroke.

OBJECTIVE

This study was to analyze the role of D-dimer in predicting clinical outcomes and mortality in patients with acute ischemic stroke.

METHODS

a. Selection and Screening

This study used the PRISMA protocol in PubMed, ScienceDirect, and Google Scholar with keywords of D-dimer, acute ischemic stroke or ischemic stroke, and clinical outcome or outcome from the inception of the database until February 2023. The downloaded articles were collected and then reviewed.

b. Eligibility Criteria

Inclusion criteria used for the literature search were: i) reporting probability (p-value, 95% CI) and odds ratio or hazard ratio; ii) obtained through predefined keywords used in the selected databases; iii) available in full-text; iv) primary studies and not a review; and v) published between 2013 and 2023. Exclusion criteria used for the literature search were: i) not primary studies; ii) not available in full-text; iii) using languages other than Indonesian and English; iv) not a research study; v) presence of other diseases or complications besides acute ischemic stroke; vi) patients with neuro-intervention procedures; and vii) recurrence of stroke.

c. Data Quality Analysis

The quality of the articles was assessed using the Newcastle-Ottawa Scale (NOS).[6]

d. Data Analysis

The statistic analysis used Review Manager software version 5.4.1. We used the inverse variance method for the random effect model with a subgroup analysis on the clinical outcome result and a fixed effect model on the mortality result. We used generic inverse variance data with a 95% confidence interval (CI). The heterogeneity of literature data will be tested using I^2. The statistically significant results are $p < 0.05$.[7]

RESULT

The PRISMA procedure was used for the systematic search, as shown in Figure 1. The three databases provided a total of 368 articles. After removing duplicates and excluding any articles, this study included eight articles.

The number of respondents, gender, age, race, onset of stroke, timing of D-dimer examination, D-dimer level, duration of follow-up, and criteria for assessing clinical outcomes using NIHSS or mRS varied among the included articles, with a total sample

of 16,107 patients. Each of these characteristics is described in detail in Table 1.

The articles were then evaluated for quality using the Newcastle-Ottawa scale, with a result range of 7-8, indicating high publication quality. These results are shown in Table 2.

The random-effect model was utilized in the clinical outcome meta-analysis in Figure 2, and the heterogeneity test, I^2, yielded a result of 56% with a p-value of 0.006. Then, the analysis was continued using a sub-group analysis by grouping for each duration of follow-up. The random effect model yielded an I^2 value of 37.4% with a p-value of 0.17.

The forest plot of clinical outcomes has a significant result for each follow-up duration. The follow-up was when discharge from hospital: OR 2.37 (95% CI 1.68–3.35); $I^2 = 45\%$ $p < 0.00001$; 1-month: OR 1.75 (95% CI 1.38–2.23), $I^2 = 47\%$ $p < 0.00001$; 3-months: OR 2.43 (95% CI 2.00-2.95), $I^2 = 0\%$ $p < 0.00001$; 6-months: OR 2.64 (95% CI 1.92–3.63), $I^2 = 0\%$ $p < 0.00001$; and 12-months: OR 1.92 (95% CI 1.31–2.82), $I^2 = 62\%$ $p < 0.0008$. Thus, there is a significant relationship between elevated D-dimer levels and worsened clinical outcomes in acute ischemic stroke patients. The result of the forest plot is shown in Figure 2.

The forest plot of mortality has a significant result with an OR of 2.25 (95% CI 1.78–2.85), $I^2 = 45\%$ $p < 0.00001$. Thus, there is a significant relationship between elevated D-dimer levels and increased mortality in acute ischemic stroke patients. The result of the forest plot is shown in Figure 3.

DISCUSSION

In the fibrinolysis system, D-dimer is the end product of cross-linked fibrin degradation by the proteolytic activity of plasmin. The fibrinolysis system is in charge of breaking down the formed fibrin to prevent blood clots from impeding blood flow. The coagulation and fibrinolysis systems are interrelated in maintaining balance. Proteases associated with vascular endothelial cells activate the plasma proenzyme plasminogen into plasmin. Plasmin dissolves cross-linked fibrin, and the end products are D-dimer and fibrin degradation products (FDPs). An increase in the D-dimer levels indicates active coagulation with ongoing thrombus formation and fibrinolysis.[3,8]

Elevated D-dimer levels are found in most patients with acute thrombosis, including acute ischemic stroke, pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation, and venous thromboembolism.[3]

The main reason why patients with acute ischemic stroke have higher levels of D-dimer level and worse clinical outcomes is that D-dimer stimulates the inflammatory response and makes monocytes release pro-inflammatory cytokines like interleukin-6 (IL-6), which cause atherogenesis, endothelial dysfunction, and hypercoagulability. IL-6 also releases tissue factor (TF), which activates the extrinsic coagulation system. As a result, recanalization is impeded, and ischemia worsens, resulting in more extensive cerebral injury and poor clinical outcomes.[9,10]

The high D-dimer cut-off values in the analyzed studies varied from 315 to 1,990 ug/l.[4,9,10,11] Regardless of value, six articles already had strict exclusion criteria.[4,5,9–12] All studies had adequate follow-up,[4,5,9–14] but two articles had more frequent follow-up at 3, 6, and 12 months after the onset of stroke.[5,12]

Variation in the cut-off values of D-dimer levels resulted in varying sensitivity and specificity results. Sensitivity values ranged between 54%–83.8%, while specificity values ranged between 41.4%– 88.9%.[4,5,9–14] Differences in cut-off values among studies cause several studies with the same variable or testing to have varying specificity values up to 24–82%.[15]

High D-dimer levels are related to all causes of death and poor clinical outcomes in acute ischemic stroke or TIA during a 1-year follow-up.[13] D-dimer levels are an independent factor as a predictor of poor clinical outcomes following an ischemic stroke at 1, 3, 6, and 12 months after stroke onset,[5,9–14] and as a predictor of mortality within 3 to 12 months after onset.[5,11,13] The study by Sato *et al.* was only conducted in patients with large vessel occlusion (LVO).[9] These results are similar to previous studies by Bao *et al*. and Zhang *et al.*, which stated that an increase in D-dimer is a predictor of worsened clinical outcomes and increased mortality.[16,17] These results are also similar to a previous study by Nezu *et al*. which revealed that a high D-dimer was related to the mortality of stroke at hospital discharge. A high D-dimer was an independent factor in all-cause mortality and recurrent stroke in cryptogenic stroke patients.[18] Hutanu *et al*, revealed that high levels of D-dimer were an independent predictor of poor outcome at 3 months after the onset of ischemic stroke.[19] A high D-dimer level is a risk marker for ischemic stroke, particularly cardioembolic stroke.[20]

According to a study by Ye N *et al*., high D-dimer levels increase the risk of poor clinical outcomes by 2.076 times but are not an independent factor. D-dimer levels predict clinical outcomes better in patients with moderate to severe stroke than in patients with mild stroke (sensitivity of 80.3% and 53.1%, respectively, with the same specificity of 88.9%).[4] Although the D-dimer level is specific for excluding patients with acute ischemic stroke, it has low sensitivity, which means that patients with acute ischemic stroke do not always have a high d-dimer level.[4]

The combination of D-dimer levels and platelet

count is a better predictor of clinical outcomes in patients than D-dimer alone, increasing the risk of mortality by 5.455 times in 3 months compared to D-dimer alone, which is 3.067 times. [5] The study by Wang J *et al*. also showed that the combination of D-dimer and total cholesterol, or LDL, is better in predicting clinical outcomes of acute ischemic stroke in 3 months, which is 2.473 and 3.280 times higher than D-dimer alone, which is 2.323 and 2.464 times.[11] The combination of D-dimer and thrombin-antithrombin levels is also better than D-dimer alone. [4]

Patients with cardioembolic stroke have a higher level of D-dimer compared to other subtypes, such as atherothrombotic and lacunar. This may be attributed to the different underlying mechanisms of thrombus formation between stroke subtypes. [4]

This study analyzed D-dimer as a predictor of clinical outcomes and mortality in patients with acute ischemic stroke using eight articles. The meta-analysis found the significant correlation between elevated D-dimer levels and worsened clinical outcomes and increased mortality in patients with acute ischemic stroke. These results suggest that D-dimer levels can be utilized to predict clinical outcomes and mortality in patients suffering from an acute ischemic stroke.

This study has the following limitations: (i) variations in the timing of D-dimer testing across studies; (ii) variations in sample characteristics; (iii) variations in criteria for assessing clinical outcomes of stroke using NIHSS or mRS; and (iv) variations in follow-up duration.

The researchers hope that future research will be conducted to analyze the relationship between the ischemic stroke subtype and the D-dimer level.

CONCLUSION

This study revealed a significant correlation between elevated D-dimer with worsened clinical outcome and increased mortality in patients with acute ischemic stroke. D-dimer would be helpful in predicting clinical outcome and mortality in patients with acute ischemic stroke since it has a long half-life, is stable, and is widely used in clinical practice. Due to the high D-dimer cut-off levels, the ideal cut-off value for estimating the sensitivity and specificity of D-dimer in predicting clinical outcome and mortality must be found in future investigations.

D-dimer levels may be more accurate in predicting clinical outcome and mortality in patients with acute ischemic stroke when combined with platelet count, thrombin-antithrombin complex, fibrinogen, neutrophil-lymphocyte ratio, total cholesterol, or LDL. However, the type of stroke is better considered in predicting clinical outcome and mortality.

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Conflict of Interest
The authors have no conflicts of interest.

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Author Contributions
PDW contributed to drafting, data extraction, data processing, editing, and administration. JH and AM performed review and monitoring. All authors read and approved the final draft.

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TABLES AND FIGURES

Table 1. Details of the included articles

References	Country	Type of study	Sample (patients)	Age (years old)	Stroke type	D-dimer record	Assessment of clinical outcome	Follow-up clinical outcome	D-dimer level (mg/l)	Clinical outcome (OR, 95% CI, p-value)	Follow-up mortality	Mortality (OR/HR, 95% CI, p-value)
Hou *et al.* 2021	China	Prospective cohort	10,518	62.3±11.4	Acute ischemic stroke or TIA	At admission < 24h	mRS 3-6	12 months	1.1 (0.6-2.1)	(OR= 1.49; 95% CI, 1.23-1.80; p < 0.001)	12 months	(HR=1.77; 95% CI, 1.25-2.52; p = 0.001)
Ye *et al.* 2020	China	Prospective cohort	236	70 (62–79)	Acute ischemic stroke	In 24h from onset	mRS ≥ 3	1 month	0.45 (0.24-0.87)	(OR: 2.076; 95% CI, 1.496-2.881; p = 0.000)	-	-
Liu *et al.* 2020	China	Prospective cohort (double blind)	1,468	63.85±12.14	Acute ischemic stroke	In 24h from onset	mRS ≥ 3 (3,6,12 month) NIHSS ≥ 5 (discharge)	Discharge (3,6,12 month)	1.83±2.29	Discharge: (OR= 2.050; 95% CI, 1.517-2.771) 3 months: (OR= 2.404; 95% CI, 1.723-3.354) 6 months: (OR= 2.383; 95% CI, 1.624-3.497) 12 months: (OR= 2.213; 95% CI, 1.415-3.461; p < 0.0001)	Hospitalization (3 months)	Hospitalization: (OR= 1.862; 95% CI, 1.000-3.466; P = 0.0007) 3 months: (OR= 3.067; 95% CI, 1.612-5.834; p < 0.0001)

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Sato *et al.* 2021	Japan	Prospective cohort	130	±7.3	Acute ischemic stroke or TIA with LVO	At admission < 24 hours	mRS 3-6	3 months	1.26 (0.6-2.8)	(OR= 3.31; 95% CI, 1.14-9.61; p = 0.028)	-	-
Wang *et al.* 2020	China	Prospective cohort	1,458	63.92±12.79	Acute ischemic stroke	In 24 hours from onset	mRS ≥ 3 (3,6,12 month) NIHSS ≥ 5 (discharge)	Discharge (3,6,12 month)	0.93±2.41	Discharge: (OR= 2.934; 95% CI, 1.914-4.500) 3 months: (OR= 3.052; 95% CI, 1.912-4.872) 6 months: (OR= 3.306; 95% CI, 1.873-5.832) 12 months: (OR= 2.828; 95% CI, 1.447-5.527; p < 0.0001)	-	-
Yang *et al.* 2014	China	Prospective cohort	220	68 (54-76)	Acute ischemic stroke	In 24 hours from onset	mRS 3-6	3 months	1.36 (0.55-3.11)	(OR= 2.18; 95% CI, 1.55-2.83; P < 0.005)	3 months	(OR= 3.22; 95% CI, 2.05-6.43; p < 0.002)

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References	Country	Type of study	Sample (patients)	Age (years old)	Stroke type	D-dimer record	Assessment of clinical outcome	Follow-up clinical outcome	D-dimer level (mg/l)	Clinical outcome (OR, 95% CI, p-value)	Follow-up mortality	Mortality (OR/HR, 95% CI, p-value)
Yao *et al.* 2019	China	Prospective cohort	877	64 (54.5-73)	Acute ischemic stroke	In 72 hours from onset	mRS 3-6	3 months	0.56 (0.24-1.79)	(OR= 2.257; 95% CI, 1.349-3.777; p < 0.002)	-	-
Wang *et al.* 2016	China	Prospective cohort	1,173	66.7±11.5	Acute ischemic stroke	At admission < 24 hours	mRS 3-6 NIHSS > 8	1 month	-	mRS: (OR= 1.604; 95% CI, 1.360-1.892; p < 0.001) NIHSS: (OR= 1.733; 95% CI, 1.461-2.056; p < 0.001)	-	-

Table 2. Assessment of Article Quality Based on The Newcastle-Ottawa Scale (NOS)

References	Selection			Comparability		Outcomes			Total
	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcomes of interest was not present at start of the study	Comparability of cohort on the basis of the design or analysis	Assessment of outcomes	Was follow-up long enough for outcomes	Adequacy of follow-up cohort	
Hou *et al.* 2021	✓	-	✓	✓	✓	✓	✓	✓	7
Ye *et al.* 2020	✓	✓	✓	✓	✓	✓	✓	✓	8
Liu *et al.* 2020	✓	-	✓	✓	✓	✓	✓	✓	7

cont...

Table 2. Assessment of Article Quality Based on The Newcastle-Ottawa Scale (NOS)

References	Selection			Comparability	Outcomes			Total
	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcomes of interest was not present at start of the study	Comparability of cohort on the basis of the design or analysis	Assessment of outcomes	Was follow-up long enough for outcomes	Adequacy of follow-up cohort	
Sato *et al.* 2020	✓	-	✓	✓	✓	✓	✓	✓	7
Wang *et al.* 2020	✓	-	✓	✓	✓	✓	✓	✓	7
Yang *et al.* 2014	✓	✓	✓	✓	✓	✓	✓	✓	8
Yao *et al.* 2019	✓	-	✓	✓	✓	✓	✓	✓	7
Wang *et al.* 2016	✓	-	✓	✓	✓	✓	✓	✓	7

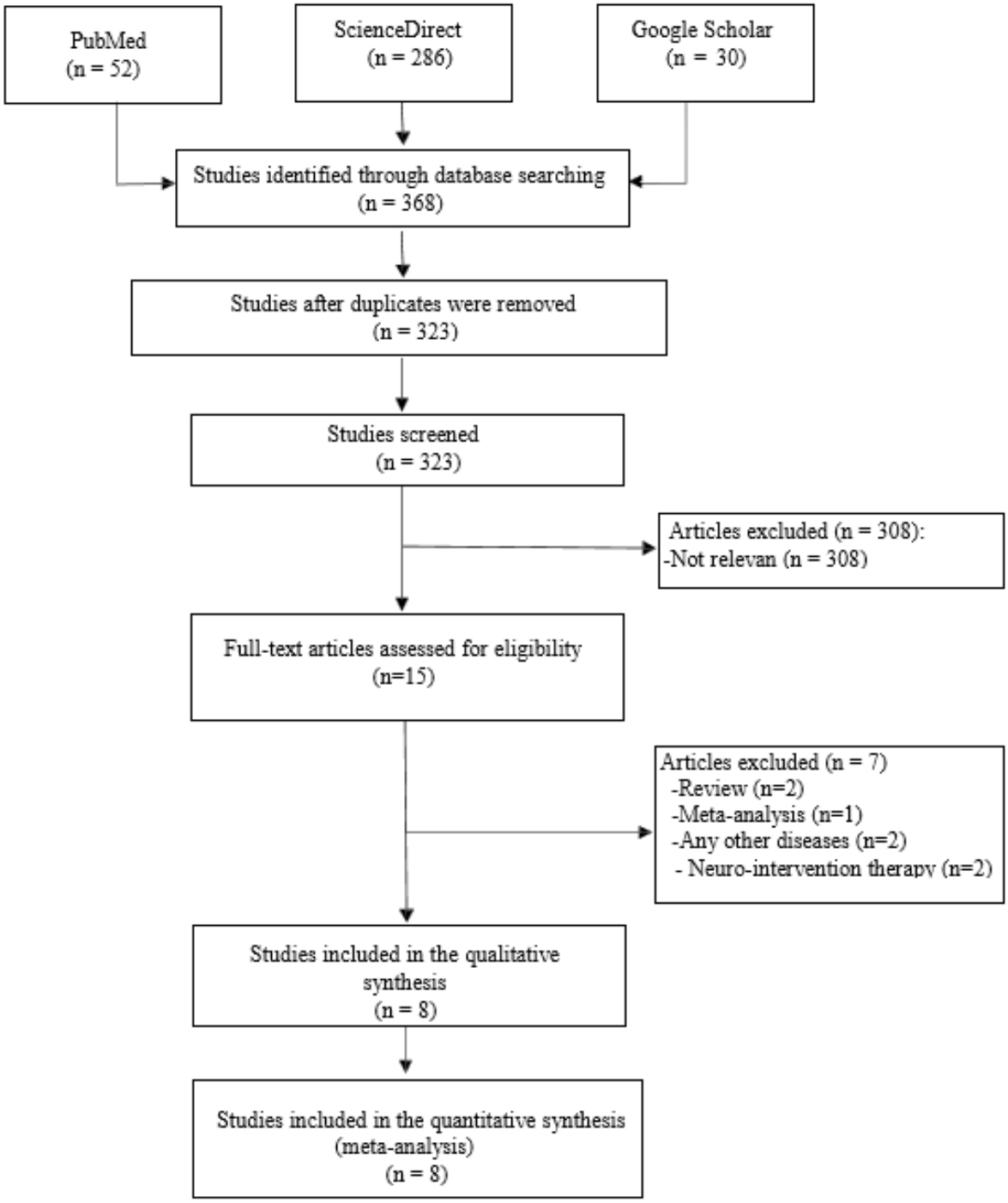

Figure 1. PRISMA Method Search Flow and Results

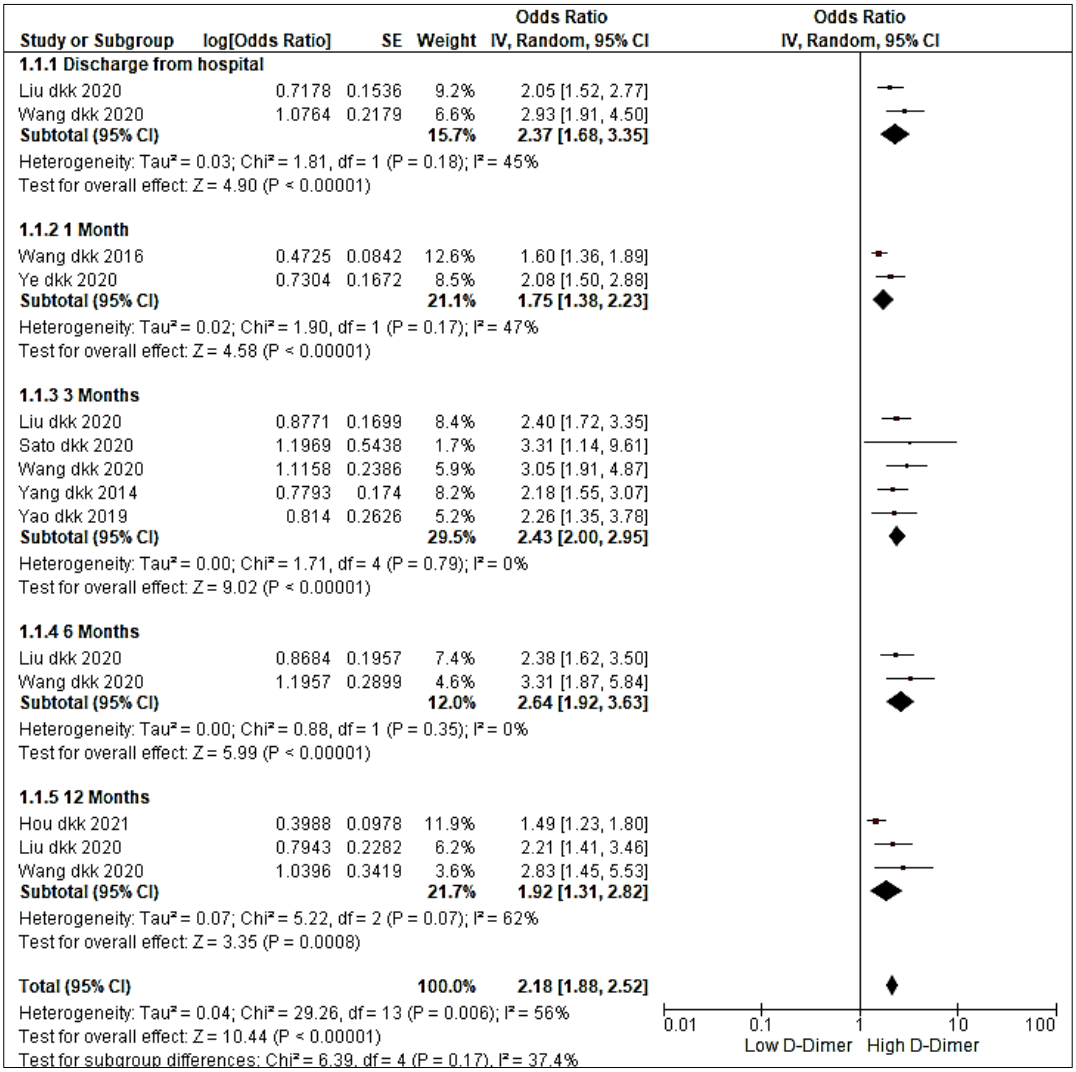

Figure 2. Forest Plot Results of D-dimer Levels on Clinical Outcome of Acute Ischemic Stroke Patients

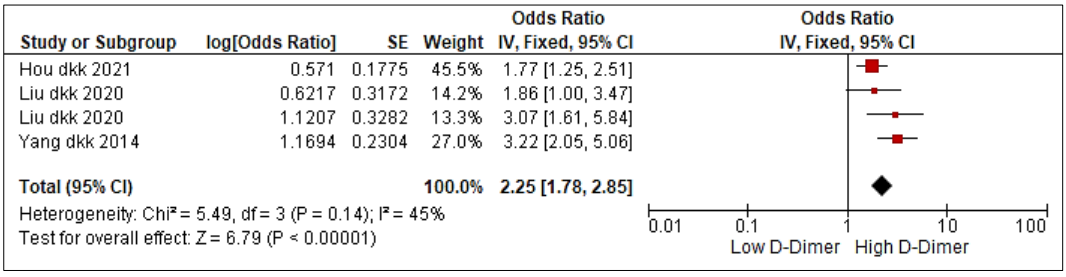

Figure 3. Forest Plot Results of D-dimer Levels on Mortality of Acute Ischemic Stroke Patients