Received: 10 December 2021 | Revised: 20 January 2022 | Accepted: 21 January 2022

DOI: 10.1002/jcla.24271

RESEARCH ARTICLE

WILEY

The correlation of D-dimer to stroke diagnosis within 24 hours: A meta-analysis

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Abstract

Background: Diagnosing D-Dimer early is essential to optimize clinical treatment and quality of life and reduce mortality. This study aims to identify the difference of D-Dimer levels (ng/ml) in patients with stroke within the 6- and 24-h period compared to patients that mimic stroke.

Methods: An electronic database search across PubMed/MEDLINE, Cochrane, Web of Science, CINAHL, EMBASE, and Scopus was conducted until December 10, 2021. Studies were eligible if they included adult patients with stroke compared to stroke mimics or controls reporting D-Dimer values. Quality assessment was conducted using GRADE. The standardized mean difference and 95% confidence intervals were calculated in addition to the difference of means in the crude form. Heterogeneity was assessed using Cochran's Q statistic and the I^2 index. A random-effects model was used. The statistical analysis was conducted using RevMan 5.4.

Results: Out of 2901, there were 318 (11%) participants from upper-middle-income countries, whereas the others were from high-income countries. Large positive effect size was found for D-Dimer in the stroke group (Cohen's $d = 2.82$ [1.73–3.9]; $p < 0.00001$), meaning that those with stroke had higher D-Dimer values on presentation compared to the stroke mimics/controls. A large difference in means was found in the two groups (MD = 685.1 [324.2, 1045.99]; $p < 0.00001$), suggesting that there was a significantly higher laboratory value in the stroke group.

Conclusion: Our findings must be used in caution as the most reliable diagnostic tests for stroke are CT and MRI. Laboratory testing such as D-Dimer values is a valuable clinical adjuvant in diagnosing total stroke.

KEYWORDS
cardiovascular, D-dimer, diagnostic, hematological, laboratory, stroke

1 | BACKGROUND

In 1970, the World Health Organization (WHO) defined stroke as "rapidly developing clinical signs of global or focal disturbance in the cerebral function that lasting more than 24 h or leading to death with no notable cause other than of vascular origin".[1] While this definition is used across the world, the WHO definition relies heavily on clinical symptoms. It is currently considered outdated by the American Stroke Association and the American Heart Association due to advances in the nature, timing, and clinical recognition of stroke and its mimics, in addition to the progressing imaging findings that require an updated definition.[2,3] The global prevalence of stroke in 2019 was reported at 101.5 million individuals, whereas ischemic stroke was reported in 77.2 million people.[4] Overall, the age-standardized stroke prevalence was highest in Southeast Asia, the Middle East, East Asia, and Oceania.[4] In 2019, 6.6 million deaths occurred due to cerebrovascular disease worldwide.[4] Further, ischemic stroke rose from 13th to 8th leading cause of global YLL (years of life lost because of premature mortality) between 1990 and 2019.[4]

Hemostasis is the property of circulation where blood retains fluidity within the vasculature, whereas the system simultaneously prevents excessive blood loss upon injury.[5] When the vascular injury occurs, clotting reactions are initiated, creating an insoluble fibrin-platelet plug at the site of the vessel wall defect, arresting blood loss, and finally restoring the vascular integrity.[6] The activation releases many substances required in platelet aggregation and initiates the coagulation cascade, leading to the formation of cross-linked fibrin, creating a clot at the injury site. During the fibrinolysis process, plasmin cleaves fibrinogen and soluble fibrin. The smallest oligomer is D-dimer.[7] On laboratory testing, the D-Dimer levels reflect the intravascular levels of fibrin turnover, confirming the plasmin and thrombin generation that has occurred.[6] When considering clinical practice, abnormal elevation of D-Dimer indicates disseminated intravascular clotting, whereas low levels aid in ruling out thromboembolic events such as pulmonary embolism and deep venous thrombosis.[8,9] While D-Dimer levels have been known to be associated with long-term mortality in the population, few studies assess the D-Dimer levels and stroke incidence.[10]

This study aims to identify the D-Dimer levels (ng/ml) in patients with stroke within the 6- and 24-h period compared to patients that mimic stroke. In this area, we conduct a meta-analysis to systematically analyze the correlation between D-dimer levels and stroke incidence.

2 | METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement 2020), clinical trials, observational studies, and case-controlled studies (five or more patients) with a stroke group and a stroke mimic/control group that reported D-Dimer values within the 24-h period were included.

2.1 | Inclusion and exclusion criteria

The following study types were included: Controlled/randomized clinical trials, retrospective or prospective cohorts, case-controlled studies with five or more patients. The studies employed adult patients aged 18 or above with no gender predilections. Studies that reported laboratory values of patients with stroke compared to stroke mimics/controls were included. All other studies were excluded.

2.2 | Search strategy

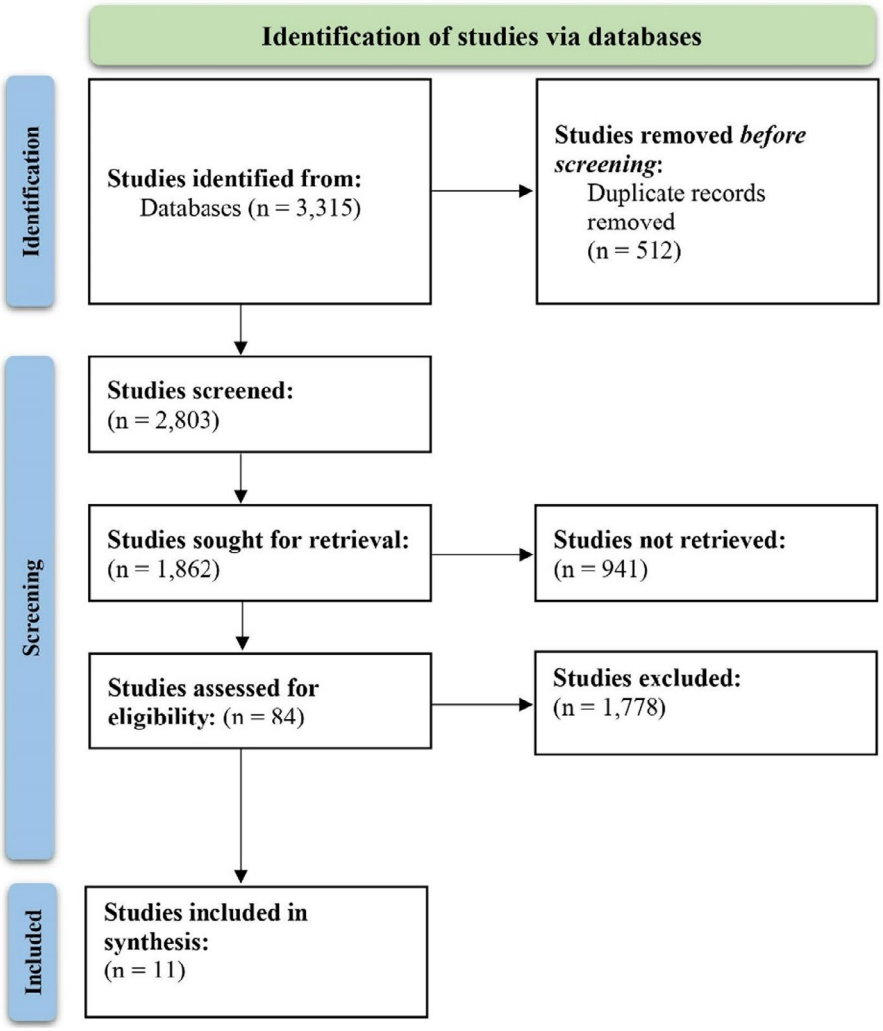
We used a systematic search strategy to assess electronic databases as per the PRISMA checklist (Figure 1). The PRISMA checklist and protocol are attached in Appendices S1 and S2. The search was conducted from inception until December 10, 2021. There were no language restrictions meaning that non-English studies were translated to English. PubMed/MEDLINE, Cochrane, Web of Science, CINAHL, EMBASE, and Scopus were searched. We manually searched SAGE, Elsevier, Science Direct, and Google Scholar to ensure no studies were missing. The reference lists of all screened were also searched (umbrella methodology). The search terms across the databases comprised the following using the BOOLEAN (and/or) logic: D-Dimer, Laboratory, Stroke, Ischemic, Hemorrhagic, Trial, and Cohort. The titles and abstracts of the screened studies were reviewed and screened independently by all reviewers. Any disagreements were resolved by active discussion. Cohen's coefficient of the agreement was computed to quantify the inter-reviewer agreement.

2.3 | Statistical analysis

The studies were stored in a bibliography management software named Endnote X9 (Clarivate Analytics). The deduplication feature was applied using the software when screening the studies. We sought to meta-analyze the means and standard deviations of D-Dimer, applying a random-effects model. These variables were continuous, and the difference in means using 95% confidence intervals was computed. Moreover, the standardized mean difference that was reported as Cohen's d with the 95% confidence interval was plotted and reported in the results. A funnel plot was utilized to test for publication bias, where we ascertained the heterogeneity between the included studies. The heterogeneity between the included studies was tested using the χ^2-based Q test and the I^2 index. A sensitivity analysis was additionally taken by removing the studies with the larges effect size and re-calculating results. The statistical analysis was conducted using Review Manager 5.4 (RevMan, Cochrane).

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework was deployed to summarize the quality of evidence by providing a systematic approach for making clinical practice recommendations. The GRADE certainty

FIGURE 1 PRISMA flowchart



ratings were tabulated to indicate the quality of evidence across the included studies.

3 | RESULTS

The overall Kappa score calculated for the inter-reviewer agreement was 0.92. In total, 3315 studies were identified from databases, of which 512 duplicates were removed. The title and abstracts of 2803 studies were screened, with 1862 studies not retrieved as they did not fit the inclusion criteria. Finally, on full-text reviewing of the 1862 studies, 84 studies were reviewed in depth. Of those, 1778 studies were excluded as they met the exclusion criteria, and 11 studies were included in the final synthesis (Figure 1). The characteristics of included studies are listed in Table 1.

Cohen's *d* effect allows us to assess the direction of effect. In this meta-analysis, a positive effect size (i.e., Cohen's *d*) indicates that the effect (i.e., Stroke presentation within the 24-h testing period using D-Dimer laboratory values) increases the mean. The interpretation we refer to for effect sizes includes small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) based on benchmarks suggested by Cohen (1988). Nine of the 11 studies reported D-Dimer values in the stroke group ($N = 1876$) and stroke mimics/control group ($N = 468$). Large positive effect size was found for D-Dimer in the stroke group (Cohen's $d = 2.82$, 95% CI = 1.73, 3.9, $p < 0.00001$), meaning that stroke patients had higher D-Dimer values on presentation compared to the stroke mimics/controls (Figure 2).

The mean difference (MD), being a standard statistic, measures the absolute difference between the mean D-Dimer value in the two groups. Nine of the 11 studies reported D-Dimer values in the two groups. A large difference in means was found in both groups (MD = 685.1, 95% CI = 324.2, 1045.99, $p < 0.00001$), meaning that there was a significantly higher laboratory value in the stroke group (Figure 3).

An analysis was conducted to note the specific changes at 24 h compared to those within 6 h, by noting Cohen's *d* effect of D-Dimer values. In the first subgroup analysis of D-Dimer values within the 6-h time frame, a medium effect size was noted D-Dimer in the stroke group (Cohen's $d = 0.49$, 95% CI = 0.29, 0.69, $p < 0.0001$) (Figure 4). In the second subgroup analysis of D-Dimer values at the 24-h time-frame, a larger positive effect size was noted for D-Dimer in the stroke group compared to within the 6-h time period (Cohen's $d = 4.19$, 95% CI = 1.77, 6.61, $p = 0.0007$) (Figure 4). The findings suggest that D-Dimer laboratory values had a medium effect size

TABLE 1 Characteristics of included studies

No.	Author, year	*n*, *N*	D-Dimer value (ng/ml)	Mean age (years)	Study design	Country
1	Bustamante et al., 2017[11]			71.95 ± 15.6	Prospective, cohort	Spain
	Patients with Stroke	463/541	6751.5 (1033.7)			
	Patients Mimicking Stroke/ Controls	78/541	6235.9 (1027.2)			
2	Knauer et al., 2012[12]			71.26 ± 15.8 and 50 ± 14.2	Prospective, cohort	Germany
	Patients with Stroke	100/149	Median = 675			
	Patients Mimicking Stroke/ Controls	49/149	Median = 322			
3	Montaner et al., 2012[13]			71.7 ± 12.25		Spain
	Patients with Stroke	337	IS = 1068.3 (1192.3); HS = 1099.2 (1383.6)			
	Patients Mimicking Stroke/ Controls	NR	NR			
4	Montaner et al., 2011a[14]			72.63 ± 12.46 and 69.57 ± 17.13	Prospective, cohort	Spain
	Patients with Stroke	915/1005	1048.1 (1188)			
	Patients Mimicking Stroke/ Controls	90/1005	722 (904.1)			
5	Meng et al., 2011[15]			58.72 ± 8.32 and 51.89 ± 7.04	Prospective, cohort	China
	Patients with Stroke	152/1005	322.57 (60.34)			
	Patients Mimicking Stroke/ Controls	46/1005	305.76 (49.52)			
6	Kavalci et al., 2011[16]			72 ± 12	Prospective, cohort	Turkey
	Patients with Stroke	HS = 29/120; IS = 71/120	HS = 1780 (3298.5); IS = 5741 (194.1)			
	Patients Mimicking Stroke/ Controls	20/120	150 (31.85)			
7	Glickman et al., 2011[17]			65.2 ± 16.2 and 50.9 ± 19.1	Prospective, cohort	USA
	Patients with Stroke	34/63	2400 (1500)			
	Patients Mimicking Stroke/ Controls	29/63	1000 (1300)			
8	Kim et al., 2010[18]			66.6 ± 11.8 and 43.8 ± 12	Prospective, cohort	Korea
	Patients with Stroke	89/146	888.1 (1289)			
	Patients Mimicking Stroke/ Controls	57/146	188.6 (113.8)			
9	Ageno et al., 2002[19]			75.7 and 75.4	Prospective, cohort	Italy
	Patients with Stroke	86/149	1740 (130)			
	Patients Mimicking Stroke/ Controls	63/149	530 (140)			

Different conditions demarcated	Time of sample collection	Methodology used	Diagnostic criteria	Length of follow-up
IS, ICH, SM	Within 6 h	Immunoassays	Stroke diagnosis was performed by trained neurologists according to the World Health Organization definition and confirmed by neuroimaging. Stroke mimic (control) diagnosis was supported with the ancillary tests deemed to be necessary in each case (i.e., EEG, lumbar puncture)	15 months
IS, SM, TIA	Within 6 h	Sandwich Fluorescence Immunoassay Technology	Clinical investigation and collection of blood samples were performed immediately after admission. This procedure was directly followed by a typical standard MRI-based stroke imaging protocol (DWI, T2*w, TOF-MRA, FLAIR, T2w, T1w, PWI)	5 months
IS, ICH	Within 24 h	ELISA	Diagnosis was made by a brain CT scan and other serial blood tests	2 years
IS, ICH, SM	Within 24 h	Sandwich ELISA	Electrocardiography, chest radiography, carotid ultrasonography, complete blood count, and leukocyte differential and blood biochemistry were performed in all patients; when indicated some patients also underwent special coagulation tests, transthoracic echocardiography, brain magnetic resonance imaging, electroencephalography, and Holter monitoring. Previously defined etiological subgroups were determined using the Trial of Org10172 in Acute Stroke Treatment criteria. Stroke was also classified according to the Oxfordshire Community Stroke Project criteria, based on clinical symptoms, location and extent of cerebral infarction. All patients underwent brain computed tomography that was reviewed by a neuroradiologist with extensive experience in acute stroke	2 years
IS, SM	Within 4.5 h	Immuno-turbidimetry assay	Symptomatic for over 1 h (s limb numbness or weakness, dyskinesia, dysphasia, balance disturbance, diplopia, dizziness/vertigo/coordination, speech/language confusion, decreased level of consciousness, headache, visual changes, and other local neurological symptoms), brain imaging findings (MRI/DWI/MRA or CTA within 24–72 h of the event)	NR
IS, ICH, HC	Within 24 h	Triage Stroke Panel	Neuroimaging testing according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria	2 years
IS, SM	Within 24 h	Specific Immunoassays	Final diagnosis of stroke was rendered by review of all clinical, imaging, and conventional laboratory data during admission	NR
IS, ICH	Within 6 h	Triage Stroke Panel	Diagnosis was made with MRI and supported by clinical signs and symptoms of focal neurologic signs/symptoms of vascular origin, with biomarker analysis	5 months
IS, TIA, HC	Within 24 h	STA Latest D-dimer assay	Computed tomographic scan of the brain and stroke subtypes defined as per the Baltimore-Washington Cooperative Young Study and the Oxfordshire Community Stroke Project	16 months

TABLE 1 (Continued)

No.	Author, year	*n*, *N*	D-Dimer value (ng/ml)	Mean age (years)	Study design	Country
10	Altès et al., 1995[20]			64 ± 10.5 and 59 ± 4.3	Prospective, cohort	Spain
	Patients with Stroke	86/146	894 (1.436)			
	Patients Mimicking Stroke/ Controls	60/146	220 (133)			
11	Takano et al., 1990[21]			64.7 and 61	Prospective, cohort	Japan
	Patients with Stroke	22/47	528.7 (94.9)			
	Patients Mimicking Stroke/ Controls	25/47	80.2 (8.4)			

Abbreviations: ICH, intracerebral hemorrhage; IS, ischemic stroke; NR, not reported; SM, stroke mimics; TIA, transient ischemic attack.

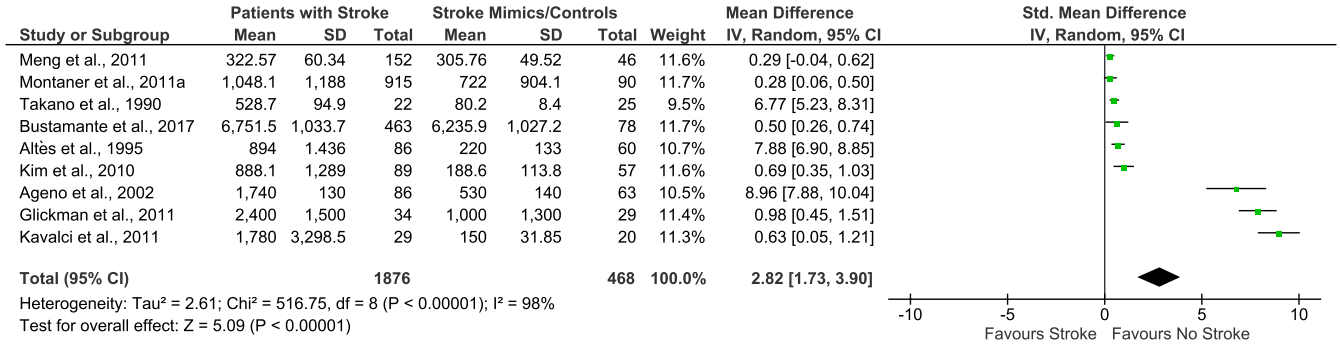


FIGURE 2 Forest plot of D-Dimer ng/ml (mean values [SD]) Stroke versus Stroke Mimics/Controls. SMD = 2.82 [95% CI = 1.73, 3.90]; Heterogeneity: $Tau^2 = 2.61$; $Chi^2 = 516.75$, df = 8 ($p < 0.00001$); $I^2 = 98\%$; Test for overall effect: $Z = 5.09$ ($p < 0.00001$)

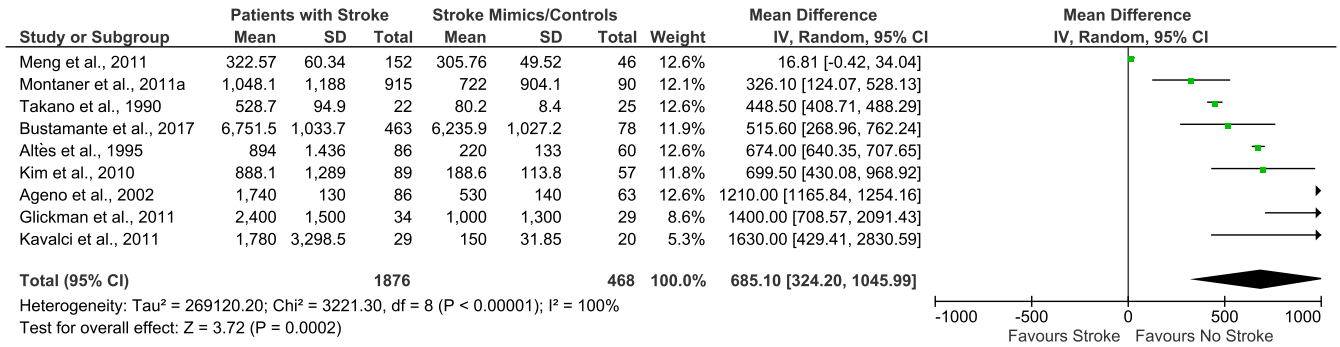


FIGURE 3 Forest plot of D-Dimer ng/ml (mean values [SD]) Stroke versus Stroke Mimics/Controls. MD = 685.1 [95% CI =324.20, 1045.99]; Heterogeneity: $Tau^2 = 269120.20$; $Chi^2 = 3221.30$, df = 8 ($p < 0.00001$); $I^2 = 100\%$; Test for overall effect: $Z = 3.72$ ($p = 0.0002$)

within the 6-h period making them a useful predictor of stroke, and that within the 24-h period, there were large effect size associations to the laboratory indicator.

Another subgroup analysis was conducted to note the differences between ELISA and other techniques. While a large effect size was found for the ELISA technique the results were insignificant (Cohen's $d = 4.95$, 95% CI = −0.86, 10.76, $p = 0.09$) (Figure 5). On sub-analyzing the other techniques, the following results were yielded: Cohen's $d = 0.56$, 95% CI = 0.36, 0.76, $p < 0.00001$) (Figure 5). Overall, the results for ELISA technique and D-Dimer values in the stroke group had a very large effect size but with the lack of significance. On the other hand, the non-ELISA techniques had a large effect size with significant findings in the stroke group of D-Dimer laboratory values.

Large heterogeneity was found in the included studies, owing to the different nature under which they were conducted. A funnel plot was created to visually inspect publication bias, as depicted in Figure 6. We found three studies deviating from an inverted funnel shape, with the other six being within a reasonable bound (Figure 6).

Different conditions demarcated	Time of sample collection	Methodology used	Diagnostic criteria	Length of follow-up
IS, HC	Within 24 h	ELISA	Diagnosis was confirmed in all cases by CT or MRI testing	8 months
IS, HC	Within 24 h	ELISA	Stroke was confirmed with electrocardiography. Brain CT and cerebral angiography were performed to confirm findings	NR

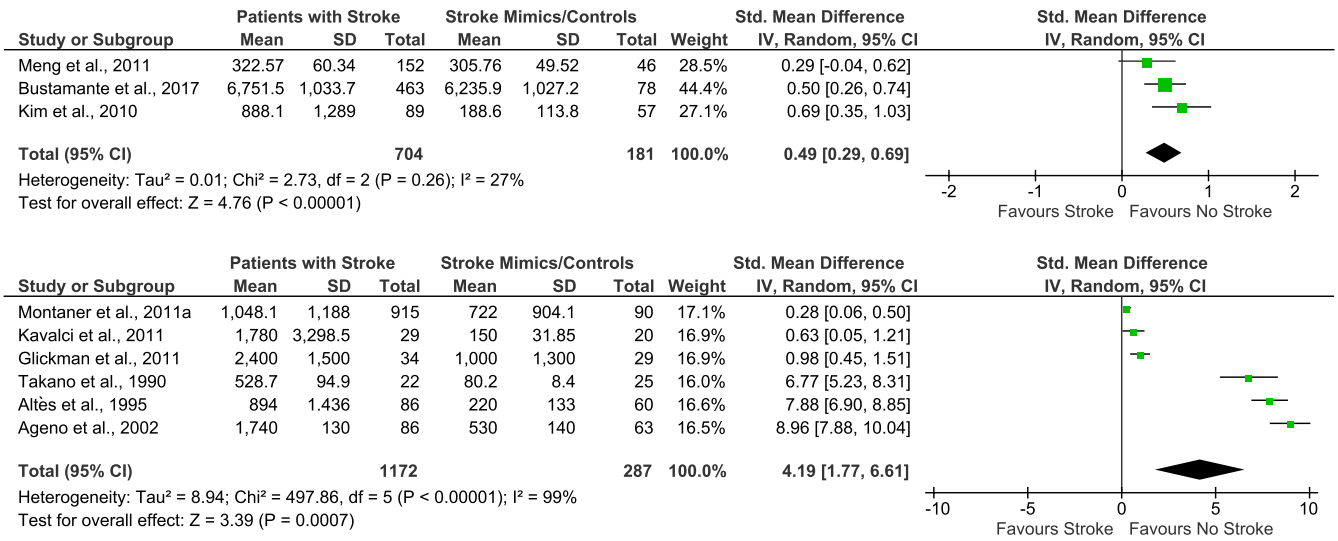


FIGURE 4 Subgroup analysis of D-Dimer ng/ml (mean values [SD]) Stroke Versus Stroke Mimics/Controls within 6 h [SMD = 0.49 [95% CI = 0.29, 0.69]; Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.73$, df = 2 ($p = 0.26$); $I^2 = 27\%$; Test for overall effect: $Z = 4.76$ ($p < 0.00001$)] (top) versus at 24 h [SMD = 4.19 [95% CI = 1.77, 6.61]; Heterogeneity: $Tau^2 = 8.94$; $Chi^2 = 497.86$, df = 5 ($p < 0.00001$); $I^2 = 99\%$; Test for overall effect: $Z = 3.39$ ($p = 0.0007$)] (bottom)

A sensitivity analysis was performed for D-Dimer outcomes applying the entire patient population for D-Dimer and SMD outcomes. As noted in Figure 2, the studies with the highest weight were Montaner et al. (2011a), Bustamante et al. (2017), Meng et al. (2011), and Kim et al. (2010). The studies were removed from the analysis to recompute findings. On removing Montaner similar findings were obtained (Cohen's $d = 3.21$ [95% CI = 1.82, 4.59] $p < 0.00001$). Similarly, on removing both Montaner and Bustamante, the findings were comparable (Cohen's $d = 3.66$ [95% CI = 1.8, 5.52], $p = 0.0001$). Then, on removing both Meng and Kim, the results were similar to the original findings (Cohen's $d = 3.59$, 95% CI = 2.03–5.14, $p < 0.00001$). The sensitivity analysis was conducted to repeat the primary analysis (SMD and D-Dimer values across all included studies); however, the moderate publication bias was arbitrary and could not be connected to the four studies with the highest weight.

The "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE) certainty scores are enlisted in Table 2. The GRADE approach was used to assess the quality of D-Dimer evidence for stroke detection across the 11 studies. Overall, eight studies had moderate GRADE certainty ratings, with two being high and one low. The evidence presented in this meta-analysis is of moderate quality. Hence, our findings must be used with caution and informed clinical application.

4 | DISCUSSION

Studies in the past have explored the role of D-Dimer as a helpful indicator in evaluating stroke patients. These studies had reported that patients with the various strokes and stroke-related diseases have acutely increased plasma D-Dimer levels.[6] Literature also supports the clinical utility of D-Dimer, a product of fibrin degradation, in the early diagnosis of stroke subtypes, in clinical practice as an extension to patients with acute cerebrovascular ischemic events.[19]

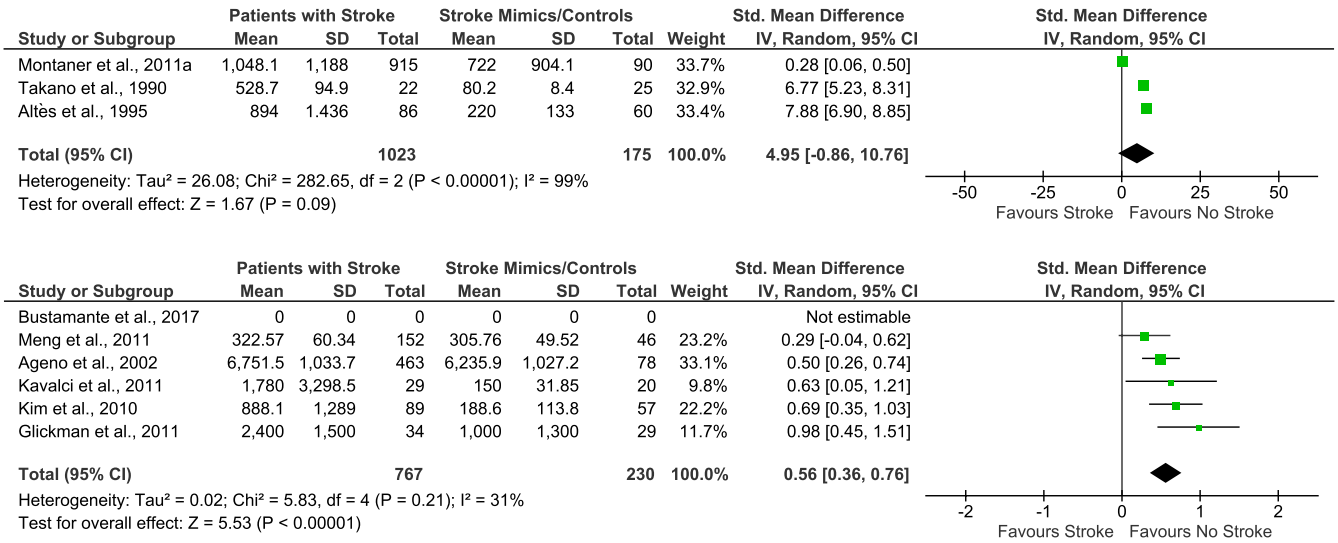


FIGURE 5 Subgroup analysis of D-Dimer ng/ml (mean values [SD]) Stroke Versus Stroke Mimics/Controls comparing ELISA [SMD = 4.95 [95% CI = −0.86, 10.76]; Heterogeneity: $Tau^2 = 26.08$; $Chi^2 = 282.65$, df = 2 ($p < 0.00001$); $I^2 = 99\%$; Test for overall effect: $Z = 1.67$ ($p = 0.09$)] (top) to all other techniques [SMD = 0.56 [95% CI = 0.36, 0.76] Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.83$, df = 4 ($p = 0.21$); $I^2 = 31\%$; Test for overall effect: $Z = 5.53$ ($p < 0.00001$)] (bottom)

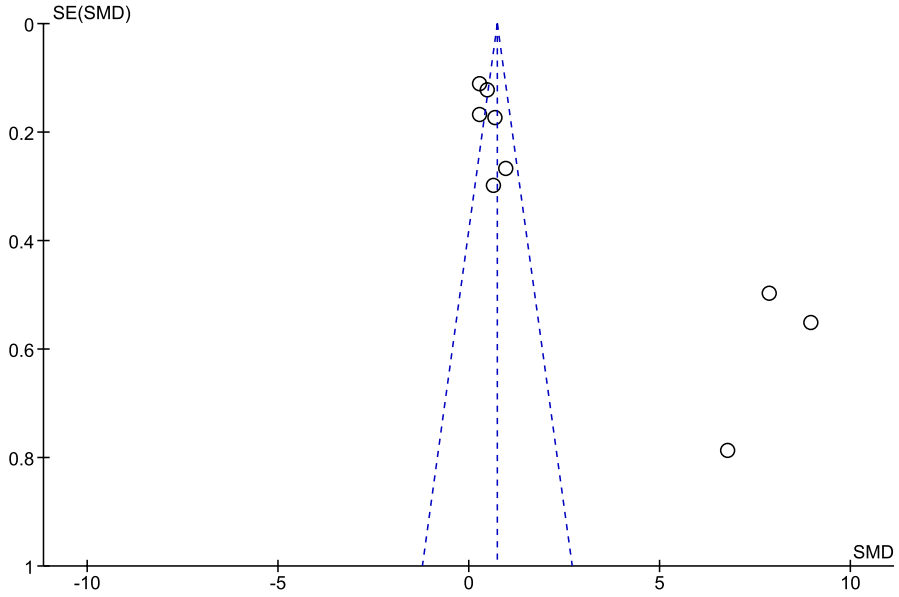


FIGURE 6 Funnel plot for the visual inspection of publication bias

While other markers such as copeptin, s100B, GFAP are also important in acute stroke, D-Dimer is considered one of the strongest markers of intravascular protein degradation, ascribed to the action of factor IIa, issue XIIIa, and fibrinolysin. In clinical practice, abnormal D-Dimer plasma levels are used as important predictors of disseminated intravascular clotting, and low levels are often used to rule out critical events such as pulmonary embolism and deep venous thrombosis.[22] Very few studies assess the role of D-Dimer with the risk of stroke of adverse clinical outcomes post-stroke.

This meta-analysis finds that patients with stroke compared to stroke mimics yielded a mean difference of 685.1 (95% CI = 324.20, 1045.99); patients with stroke had a higher laboratory value of D-Dimer on testing. Moreover, a large positive effect size was found for D-Dimer in the stroke group (d = 2.82, 95% CI = 1.73, 3.9), wherein stroke patients had higher D-Dimer values on presentation compared to the stroke mimics/controls. The majority of the studies were conducted within a 24-h period, while three were completed within a 6-h timeframe, with only one done in the 4.5-h period.

While several observational studies report associations between D-Dimer levels and the incidence of stroke, the findings have been inconsistent so far.[23–25] Yuan and colleagues analyzed the associations between D-Dimer and the risk of stroke (i.e., pre-stroke) employing a sample set of 22,590 patients.[22] The authors found that the D-Dimer levels increased the risk of total stroke by 40% (RR = 1.4, 95% CI = 1.2–1.63).[22] In our study, we found a large positive effect size of D-Dimer levels among patients who were diagnosed with stroke using laboratory testing as an adjuvant to imaging findings (Cohen's d = 2.82, 95% CI = 1.73–3.9). Yuan et al. also noted that

when the D-Dimer level increased by 50 ng/ml, the risk of stroke increased by 0.3%.[22]

The two imaging tests allow a clear view of the head, including the blood vessels and tissue, including computed tomography (CT), scans, and magnetic resonance imaging (MRI). The average cost of a CT scan in the United States is $3275 ($300–$6750), compared to around $80 ($40–$250) in Pakistan.[26,27] The price of an MRI in the United States is $1325 ($375–$2850), whereas, in Pakistan, the reported price is around $10 ($4–$45).[26,27] In the United States, the average D-Dimer test cost ranges between $239 and $303,[28] whereas in Pakistan, it costs around $8–$14 for the test.[29] While Pakistan and the United States have been used as case studies to review test prices in LMIC and HIC, respectively, it is essential to note that access to CT and MR scanners is a critical prerogative. For instance, urban centers in LMIC are known to have a large proportion of CT and MRI scanners, whereas rural centers may have limited access to facilities.[30]

The annual number of deaths due to strokes increased substantially from 1990 to 2019, despite the reductions in age-standardized rates, specifically in the 70 and above age group. The highest number of age-standardized stroke-related mortality and DALY rates belonged to the low-income countries as per the World Bank classification.[31] We posit that without the implementation of primary prevention strategies and cheap "filtering" tests available at primary care centers, the stroke burden will continue to rise across the world, particularly in low- and middle-income countries. In our meta-analysis, only two upper-middle-income countries were represented, whereas the other nine were HIC (Figure 7).

TABLE 2 GRADE certainty rating of all included studies

Author, year	GRADE certainty ratings
Bustamante et al., 2017[11]	High
Knauer et al., 2012[12]	Moderate
Montaner et al., 2012[13]	Moderate
Montaner et al., 2011a[14]	Moderate
Meng et al., 2011[15]	Moderate
Kavalci et al., 2011[16]	Low
Glickman et al., 2011[17]	High
Kim et al., 2010[18]	Moderate
Ageno et al., 2002[19]	Moderate
Altès et al., 1995[20]	Moderate
Takano et al., 1990[21]	Moderate

4.1 | Strengths and limitations

The findings from this meta-analytical study can help guide evidence-based healthcare planning and resource allocation for stroke across LMIC and HIC by prioritizing measures to diagnose it within the 6-h period. The findings from this meta-analysis have summarized the results of D-Dimer among patients that have confirmed stroke and compared it to stroke mimics in a comprehensive manner. To ensure the best quality evidence, we computed mean differences and SMD to ensure that we do not synthesize the risk estimates only, stabilizing our results. These findings provide a state-of-the-art understanding of how D-Dimer may be applicable across LMIC in primary care centers and in diagnosing stroke.

There are certain limitations in this meta-analysis. First, we could not differentiate results based on the different stroke types because of the paucity of data. Second, the number of included studies was limited due to the lack of reported data from LMIC. Third, we could not account for confounding factors as the study populations were not demarcated in the included studies. Finally, racial data were not aligned to the clinical outcomes; hence, a racial-specific meta-analysis could not be undertaken.

5 | CONCLUSION

Based on our study discoveries, high D-Dimer levels are strongly correlated to a stroke diagnosis. There is no evidence for the different stroke types, and our clinical applications are limited to total stroke incidences. The quantification of D-Dimer levels across the different stroke subtypes and TIA must be substantiated to corroborate our findings.

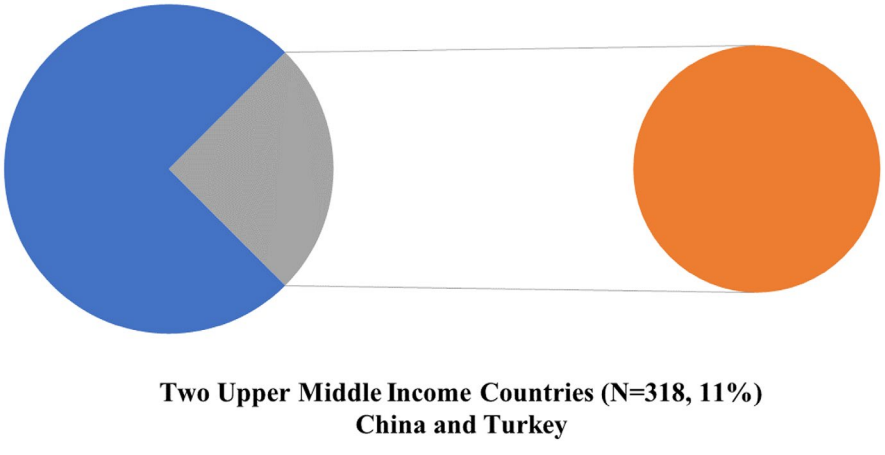


FIGURE 7 The countries represented in this meta-analysis. In total, 318 out of 2901 participants were from upper-middle-income countries (11%; China and Turkey). The majority of participants ($N = 2583$) were from high-income countries (89%, Spain, Germany, USA, Korea, Italy, Japan)

CONFLICT OF INTEREST

The authors completed the ICMJE Unified Competing Interest form (available upon request from the corresponding author) and declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data used and acquired for this study are available online.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ahmad A, Islam Z, Manzoor Ahmad S, et al. The correlation of D-dimer to stroke diagnosis within 24 hours: A meta-analysis. *J Clin Lab Anal*. 2022;36:e24271. doi:10.1002/jcla.24271