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

Adeel Ahmad | Zara Islam | Saad Manzoor Ahmad | Zouina Sarfraz | Azza Sarfraz | Miguel Felix | Ivan Cherrez-Ojeda

1 Shalamar Medical and Dental College, Lahore, Pakistan
2 Sahiwal Medical College, Sahiwal, Pakistan
3 CMH Lahore Medical College & Institute of Dentistry, Lahore, Pakistan
4 Fatima Jinnah Medical University, Lahore, Pakistan
5 The Aga Khan University, Karachi, Pakistan
6 Universidad Espíritu Santo, Samborondón, Ecuador
7 Respiralab Research Center, Guayaquil, Ecuador

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”. 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. The global prevalence of stroke in 2019 was reported at 101.5 million individuals, whereas ischemic stroke was reported in 77.2 million people. Overall, the age-standardized stroke prevalence was highest in Southeast Asia, the Middle East, East Asia, and Oceania. In 2019, 6.6 million deaths occurred due to cerebrovascular disease worldwide. 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.

Hemostasis is the property of circulation where blood retains fluidity within the vasculature, whereas the system simultaneously prevents excessive blood loss upon injury. 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. 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. On laboratory testing, the D-Dimer levels reflect the intravascular levels of fibrin turnover, confirming the plasmin and thrombin generation that has occurred. 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. 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.

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 bibliographic 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 $I^2$-based Q test and the $I^2$ index. A sensitivity analysis was additionally taken by removing the studies with the larger effect size and re-calculating the 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...
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, $p < 0.00001$) (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.
| No. | Author, year | n, N | D-Dimer value (ng/ml) | Mean age (years) | Study design | Country |
|-----|--------------|------|-----------------------|------------------|--------------|---------|
| 1   | Bustamante et al., 2017<sup>17</sup> |     |                       |                  |             |         |
|     | Patients with Stroke                  | 463/541 | 6751.5 (1033.7)   | 71.95 ± 15.6  | Prospective, cohort | Spain    |
|     | Patients Mimicking Stroke/ Controls   | 78/541  | 6235.9 (1027.2)   |                  |             |         |
| 2   | Knauer et al., 2012<sup>12</sup>     |     |                       |                  |             |         |
|     | Patients with Stroke                  | 100/149 | Median = 675        | 71.26 ± 15.8 and 50 ± 14.2 | Prospective, cohort | Germany |
|     | Patients Mimicking Stroke/ Controls   | 49/149  | Median = 322        |                  |             |         |
| 3   | Montaner et al., 2012<sup>13</sup>   |     |                       |                  |             |         |
|     | Patients with Stroke                  | 337   | IS = 1068.3 (1192.3); HS = 1099.0 (1383.6) | 71.7 ± 12.25   |             | Spain   |
|     | Patients Mimicking Stroke/ Controls   | NR    | NR                   |                  |             |         |
| 4   | Montaner et al., 2011<sup>14</sup>   |     |                       |                  |             |         |
|     | Patients with Stroke                  | 915/1005 | 1048.1 (1188)       | 72.63 ± 12.46 and 69.57 ± 17.13 | Prospective, cohort | Spain   |
|     | Patients Mimicking Stroke/ Controls   | 90/1005 | 722 (904.1)           |                  |             |         |
| 5   | Meng et al., 2011<sup>15</sup>       |     |                       |                  |             |         |
|     | Patients with Stroke                  | 152/1005 | 322.57 (60.34)       | 58.72 ± 8.32 and 51.89 ± 7.04 | Prospective, cohort | China   |
|     | Patients Mimicking Stroke/ Controls   | 46/1005 | 305.76 (49.52)         |                  |             |         |
| 6   | Kavalci et al., 2011<sup>16</sup>    |     |                       |                  |             |         |
|     | Patients with Stroke                  | HS = 29/120; IS = 71/120 | HS = 1780 (3298.5); IS = 5741 (194.1) | 72 ± 12          | Prospective, cohort | Turkey  |
|     | Patients Mimicking Stroke/ Controls   | 20/120 | 150 (31.85)           |                  |             |         |
| 7   | Glickman et al., 2011<sup>17</sup>   |     |                       |                  |             |         |
|     | Patients with Stroke                  | 34/63  | 2400 (1500)           | 65.2 ± 16.2 and 50.9 ± 19.1 | Prospective, cohort | USA     |
|     | Patients Mimicking Stroke/ Controls   | 29/63  | 1000 (1300)          |                  |             |         |
| 8   | Kim et al., 2010<sup>18</sup>        |     |                       |                  |             |         |
|     | Patients with Stroke                  | 89/146 | 888.1 (1289)         | 66.6 ± 11.8 and 43.8 ± 12 | Prospective, cohort | Korea   |
|     | Patients Mimicking Stroke/ Controls   | 57/146 | 188.6 (113.8)         |                  |             |         |
| 9   | Ageno et al., 2002<sup>19</sup>      |     |                       |                  |             |         |
|     | Patients with Stroke                  | 86/149 | 1740 (130)             | 75.7 and 75.4    | Prospective, cohort | Italy   |
|     | 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 |
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 insigificant (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).

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

### Table 1 (Continued)

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

### 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. 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
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 cloting, and low levels are often used to rule out critical events such as pulmonary embolism and deep venous thrombosis. 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. 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. 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). 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 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).

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.

**TABLE 2** GRADE certainty rating of all included studies

| Author, year       | GRADE certainty ratings |
|--------------------|-------------------------|
| Bustamante et al., 201711 | High                  |
| Knauer et al., 201212    | Moderate               |
| Montaner et al., 201213  | Moderate               |
| Montaner et al., 201114  | Moderate               |
| Meng et al., 201115    | Moderate               |
| Kavalci et al., 201116  | Low                    |
| Glickman et al., 201117 | High                   |
| Kim et al., 201018     | Moderate               |
| Ageno et al., 200219   | Moderate               |
| Altès et al., 199520   | Moderate               |
| Takano et al., 199021  | Moderate               |

**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.

ORCID
Zouina Sarfraz https://orcid.org/0000-0002-2243-3646
Azza Sarfraz https://orcid.org/0000-0001-8206-5745
Miguel Felix https://orcid.org/0000-0002-2243-3646
Ivan Cherrez-Ojeda https://orcid.org/0000-0002-1610-239X

REFERENCES
1. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaboration. Bull World Health Organ. 1980;58(1):113.
2. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-2089.
3. Coupland AP, Thapar A, Qureshi MI, Jenkins H, Davies AH. The definition of stroke. J R Soc Med. 2017;110(9):7-12.
4. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association Circulation. 2021;143(8):e254-e743.
5. Hoffman M, Monroe DM III. A cell-based model of hemostasis. Thromb Haemost. 2001;85(6):958-965.
6. Haapaniemi E, Tatlisumak T. Is D-dimer helpful in evaluating stroke patients? A systematic review. Acta Neurol Scand. 2009;119(3):141-150.
7. Lip GYH, Lowe GDO. Fibrin D-dimer: a useful clinical marker of thrombogenesis? Clin Sci. 1995;89(3):205-214.
8. Taylor HA Jr, Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn Dis. 2005;15(4 Suppl 6):S6-S4.
9. Sarfraz A, Sarfraz Z, Razzack AA, Patel G, Sarfraz M. Venous Thromboembolism, Corticosteroids and COVID-19: A Systematic Review and Meta-Analysis. Clin Appl Thromb Hemost. 2021;2021:1076029621993573.
10. Lowe GDO. Fibrin D-dimer and cardiovascular risk. In: Seminars in Vascular Medicine. Copyright© 2005 by Thieme Medical Publishers, Inc.; 2005:387-398.
11. Bustamante A, Lopez-Cancio E, Pich S, et al. Blood biomarkers for the early diagnosis of stroke: the stroke-chip study. Stroke. 2017;48(9):2419-2425.
12. Knauer C, Knauer K, Müller S, et al. A biochemical marker panel in MRI-proven hyperacute ischemic stroke—a prospective study. BMC Neurol. 2012;12(1):7.
13. Montaner J, Mendioroz M, Delgado P, et al. Differentiating ischemic from hemorrhagic stroke using plasma biomarkers: the S100B/RAGE pathway. J Proteomics. 2012;75(15):4758-4765.
14. Montaner J, Mendioroz M, Ribó M, et al. A panel of biomarkers including caspase-3 and D-dimer may differentiate acute stroke from stroke-mimicking conditions in the emergency department. J Intern Med. 2011;270(2):166-174.
15. Meng R, Li ZY, Ji X, Ding Y, Meng S, Wang X. Antithrombin III associated with fibrinogen predicts the risk of cerebral ischemic stroke. Clin Neurol Neurosurg. 2011;113(5):380-386.
16. Kavalci C, Gencelallac H, Durukan P, Cevik Y. Value of biomarker-based diagnostic test in differential diagnosis of hemorrhagic-ischemic stroke. Bratisl Lek Listy. 2011;112(7):399-401.
17. Glickman SW, Phillips S, Anstrom KJ, Laskowitz DT, Cairns CB. Discriminative capacity of biomarkers for acute stroke in the emergency department. J Emerg Med. 2011;41(3):333-339.
18. Kim MH, Kang SY, Kim MC, Lee WI. Plasma biomarkers in the diagnosis of acute ischemic stroke. Ann Clin Lab Sci. 2010;40(4):336-341.
19. Ageno W, Finazzi S, Steidl L, et al. Plasma measurement of D-dimer levels for the early diagnosis of ischemic stroke subtypes. Arch Intern Med. 2002;162(22):2589-2593.
20. Altes A, Mbellâen MT, Mateo J, Avila A, Martí-Vialalta JL, Fontcuberta J. Hemostatic disturbances in acute ischemic stroke: a study of 86 patients. Acta Haematol. 1995;94(1):10-15.
21. Takano K, Yamaguchi T, Kato H, Omae T. Activation of coagulation in acute cardioembolic stroke. Stroke. 1991;22(12):1-16.
22. Yuan B, Yang T, Yan T, Cheng W, Bu X. Relationships between D-dimer levels and stroke risk as well as adverse clinical outcomes after acute ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Front Neurol. 2021;12:792.
23. Di Castelnuovo A, Agnoli C, de Curtis A, et al. Elevated levels of D-dimers increase the risk of ischaemic and haemorrhagic stroke. Thromb Haemost. 2014;112(11):941-946.
24. Folsom AR, Gottesman RF, Appiah D, Shahar E, Mosley TH. Plasma D-dimer and incident ischemic stroke and coronary heart disease: the atherosclerosis risk in communities study. Stroke. 2016;47(1):18-23.
25. Wannamethee SG, Whincup PH, Lennon L, Rumley A, Lowe GD. Fibrin D-dimer, tissue-type plasminogen activator, von Willebrand factor, and risk of incident stroke in older men. Stroke. 2012;43(5):1206-1211.
26. Medical Procedure & Facility Cost, Procedure Information for Patients [Internet]. [cited 2021 Dec 11]. https://www.newchoicel health.com/
27. Oladoc. Oladoc Services [Internet]. 2021 [cited 2021 Dec 11]. https://oladoc.com/
28. Dx saver. Get lowest D dimer test cost at $239|normal range, and more [Internet]. 2021 [cited 2021 Dec 11]. https://www.dxsaver.com/d-dimer-test-cost/
29. Instacare. D-dimer test-Instacare. [Internet]. 2021 [cited 2021 Nov 11]. https://instacare.pk/book-tests/d-dimer
30. Farooq A, Venketasubramanian N, Wasay M. Stroke care in Pakistan. Cerebrovasc Dis Extra. 2021;11(3):118-121.
31. The World Bank. Total Population - South Asia [Internet]. [cited 2021 Dec 11]. https://www.worldbank.org/en/region/sar/overview#1

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

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