Correlation between D-Dimer Level and Ischemic Stroke in COVID-19 Patients in Rajavithi Hospital

Abstract

Introduction: COVID-19 may lead to abnormal blood clots and ischemic stroke. The mechanism is a hypercoagulable state, with elevated D-dimer levels seen in COVID-19-infected patients, resulting from activation of both the coagulation and innate immune systems. D-dimer levels are known to increase in patients with severe COVID-19 infections.

Objectives: 1. To study the correlation between D-dimer levels and acute ischemic stroke in COVID-19 patients. 2. To study any factors associated with acute ischemic stroke in COVID-19 patients.

Materials and Methods: Retrospective case-control study used collected data from Covid-19 patient admitted to the Covid-19 ward in Rajavithi Hospital during July 1, 2020 - June 30, 2022.

Results: 25 patients of 18,586 COVID-19 patients had acute ischemic stroke, representing 0.13% of the total. D-dimer and hs-CRP levels showed no significant difference between the two groups. There is no significant relationship between high D-dimer levels and ischemic stroke events in COVID-19 patients. However, the study found that increase in diastolic blood pressure reduced the risk of ischemic stroke by 7% (p=0.01) and the use of antiplatelet medication was found to decrease the risk of ischemic stroke by 82% (p=0.046).

Conclusion: There is no significant relationship between high D-dimer levels and ischemic stroke events in COVID-19 patients. However, the study's conclusions may be limited by the small sample size and short duration of observation and follow-up. Further research with larger study populations and longer observation periods is needed.

Pairat Yangkitwiboon, Sirikanlaya Poonphol

Pairat Yangkitwiboon, Sirikanlaya Poonphol
Neurology unit, Department of Medicine, Rajavithi Hospital

Corresponding author:
Pairat Yangkitwiboon
Neurology unit, Department of Medicine, Rajavithi Hospital
E-mail: pairatzen1@gmail.com

Introduction

COVID-19 is a disease caused by the SARS-CoV-2 virus that primarily affects the respiratory system, but it has also been found to cause abnormal blood clots and increase the risk of ischemic stroke in people with underlying health conditions.[1] These complications can lead to an increased risk of death in COVID-19 patients.[2, 3] A study of 138 COVID-19 cases in Wuhan, China found that patients with critical conditions often had underlying health conditions such as high blood pressure (58%), diabetes (22%), coronary heart disease (25%), and stroke (17%). The study also found that patients over 60 years of age had a higher risk of death.[3, 4] The deaths of patients from COVID-19 were associated with a hypercoagulable state, pro-inflammatory response and elevated levels of biomarkers such as C-reactive protein, D-dimer, and ferritin. The study also found that 2-6% of patients with COVID-19 infection had stroke complications.[5]

Research suggests that the incidence of abnormal neurological symptoms in COVID-19 infected patients may be as high as 36%. A study in China reported that the incidence of acute stroke in patients with severe COVID-19 was 5.7%, and in patients with non-severe disease was 0.8% (p=0.03).[6] A study conducted in New York by Yaghi et al found that 0.9% of all patients hospitalized with COVID-19 experienced ischemic stroke.[7] These studies suggest that COVID-19 infection may increase the risk of stroke.

D-dimer is a marker of the degradation of vascular proteins involved in coagulation. Elevated levels of D-dimer have been found in COVID-19 patients experiencing acute ischemic stroke[7, 9, 10],

suggesting activation of the coagulation and innate immune system.[11, 12] Studies have also shown that D-dimer levels are more significantly elevated in patients with severe COVID-19.

This study examines the relationship between elevated D-dimer levels and acute ischemic stroke in COVID-19 patients at Rajavithi hospital.

Objective

1. The study aims to investigate the correlation between D-Dimer levels and acute ischemic stroke in COVID-19 patients.

2. The study aims to investigate any factors associated with acute ischemic stroke in COVID-19 patients.

Materials and Methods

Study Design

A retrospective case-control study used collected data from COVID-19 patients admitted to the COVID-19 ward in Rajavithi Hospital during July 1, 2020 - June 30, 2022.

Characteristics of study samples

The sample group was all COVID-19-infected patients with acute ischemic stroke compared with 25 COVID-19-infected patients without ischemic stroke. Both groups were admitted to the COVID-19 ward at Rajavithi Hospital between July 1, 2020, and June 30, 2022.

Inclusion criteria

- Age 18 and over.

- Infected with COVID-19 diagnosed by laboratory testing nasopharyngeal swab by RT-PCR, ATK.

- Have blood test results according to the COVID-19 protocol, including CBC, LFT, BUN, Cr,

Ca, Mg, PO4, hs-CRP, D-dimer, LDH, and Lactate that collect the day of diagnosis.

- Ischemic stroke was diagnosed from the signs and symptoms of permanent and acute neurological loss suggestive of ischemic stroke and/or brain CT scan results.

- Have blood test results for FBS, HbA1C, LDL, HDL, Triglyceride, and Total cholesterol

Exclusion criteria

- Incomplete or missing treatment history information in the medical record. - Conditions that resulted in false positives and false negatives on D-dimer and CRP level; accident history 1 month before illness, patients with cancer, and patients with a history of ischemic stroke or ischemic heart disease less than 1 month, patients with a hypercoagulable state, pregnant patients, patients with pulmonary embolism.

Sample Size

In this research, the sample size was calculated by using the ratio comparison formula of 2 groups[15].

$$n = \frac{[Z_{\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + Z_{\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}]^2}{(P_1 - P_2)^2}$$

n = number of sample sizes for each group

$Z_{\alpha/2}$ = Statistical value under the standard curve when determining the level of statistical significance α = 0.05 is 1.96

Z_{β} = The statistical value under the standard curve when given the 80% testpowerlevel is 0.842.

P_1 = High levels of D-dimer were found among COVID-19 patients. with no ischemic stroke 76%, p_1 =0.76[16]

P_2 = High levels of D-dimer were found among COVID-19 patients caused by cerebrovascular accident estimated from a study by Anzej S et al. It was found that high D-dimer levels are a risk factor for ischemic stroke (RR 3.9)[16]

p_2=p_1*RR/(1+p_1*RR-1) = 0.76*3.9/ (1+0.76*3.9-1) = 0.925

$\bar{P}$= Mean levels of d-dimer found in both groups $=\dfrac{(P_1 + P_2)}{2} = 0.843$

Therefore, the number of samples can be calculated as follows.

$$n = \frac{[1.96\sqrt{2(0.843)(1-0.843)}+0.842\sqrt{0.76(1-0.76)+0.925(1-0.925)}]^2}{(0.76-0.925)^2}$$

$n = 76$ +missing data 10%
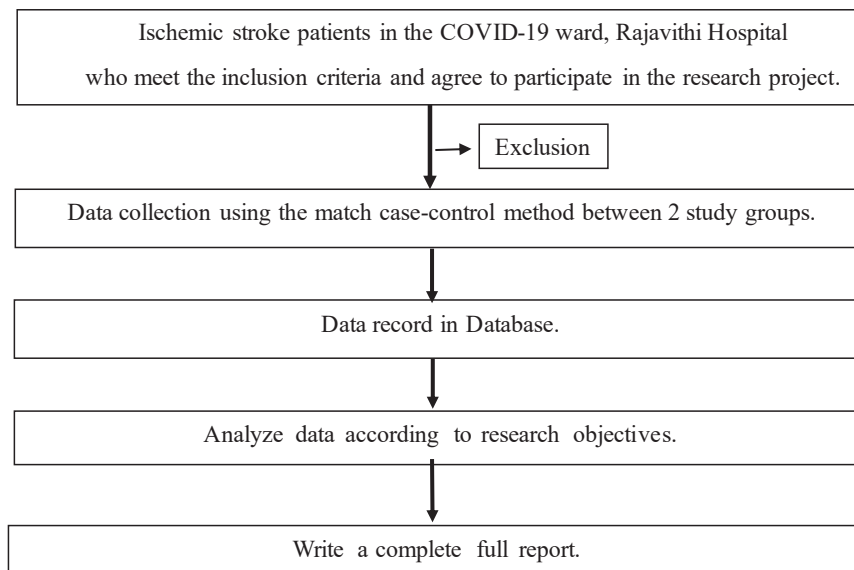$= 85$

Therefore, in this study, the researcher will collect data from 85 subjects, including 2 groups, totaling 170 subjects using the match case-control method between 2 study groups by age, gender, the severity of COVID-19 infection, and underlying disease to decrease the confounder.

During the data collection process, we can collect only 25 COVID-19 patients with acute ischemic stroke.

Methodology

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│   Ischemic stroke patients in the COVID-19 ward, Rajavithi    │
│                        Hospital                                │
│  who meet the inclusion criteria and agree to participate     │
│                 in the research project.                       │
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│  Data collection using the match case-control method          │
│                 between 2 study groups.                        │
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│                   Data record in Database.                     │
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Statistical Analysis

Descriptive Statistics

The categorical data is reported by percentage. Continuous data with normal distribution is reported as means and standard deviation. If the data is not a normal distribution data, it is reported with median, minimum, maximum, and interquartile range, and percentile rank.

Inferential Statistics

Categorical data were compared using the Chi-square test or Fisher's exact test or McNemar test. The uncorrelated data is compared with Student t-test for normal distribution data and Mann-Whitney U-test was used for non-normal distribution data. Binary Logistic regression was used for correlation factor analysis and risk was reported by OR (95% CI). Determination of the cut-off point for screening or diagnosis using the curve (ROC curve) and presented by AUC (Area under the curve). All tests were assigned a level of statistical significance at a p-value < 0.05.

Results

The number of COVID-19 patients admitted to the COVID-19 ward at Rajavithi Hospital between July 1, 2020, and June 30, 2022, totaled 18,586. There were 25 patients with acute ischemic stroke, representing 0.13%.

Table 1 demonstrates the baseline characteristics, medication, severity of Covid-19 infection, and laboratory testing. Among individuals in the protocol, COVID-19 patients with acute ischemic stroke, 64% are male, and the mean age is 65.12 years (SD 12.19). In COVID-19 patients without acute ischemic stroke, 72% are male, and the mean age is 64.2 years (SD 12.05). There is no statistically significant difference between age (p=0.790), gender (p=0.544), BMI (p=0.346), smoking, and underlying diseases (p=0.107) among the groups.

As shown in Table 3, lacunar stroke is the primary stroke etiology in this study (56%), with an average NIHSS score of 6.96±5.12. There is no statistically significant difference between the severity of COVID-19 infection among the two

groups (p=0.481). Other vital signs and oxygen saturation at room air have no statistically significant difference between the two groups.

There is no statistically significant difference between D-Dimer (p=0.334) and hs-CRP (p=0.431) among the two groups. There is no significant relationship between high D-dimer levels and ischemic stroke events in COVID-19 patients.

Another laboratory test also has no statistically significant difference between the two groups.

The protective factors among the two groups are aspirin usage and low diastolic blood pressure, as shown in Table 2. Increased every 1 mmHg decreased the risk of ischemic stroke by 7% (p= 0.008). Antiplatelet medication usage reduced the risk of ischemic stroke by 82% (p-value = 0.046)

Table 1 Demographic data of COVID-19 patients (n = 50)

Demographic	Stroke patient (n = 25)	Non-Stroke patient (n = 25)	p-value
Sex			0.544
Male	16 (64.0)	18(72.0)	
Female	9 (36.0)	7 (28.0)	
Age (years)	65.12±12.19	64.2±12.05	0.790
BMI (kg/m2)	25.65±5.33	23.82±6.44	0.346
Smoking			0.200
Non-smoke	19 (76.0)	22(72.0)	
Previous smoke	3 (12.0)	0(72.0)	
Current smoke	3 (12.0)	3(72.0)	
Underlying disease	16 (64.0)	21 (84.0)	0.107
DM	6 (37.5)	9 (42.9)	0.355
Hypertension	10 (62.5)	14 (66.7)	0.258
Dyslipidemia	7 (43.8)	3 (14.2)	0.157
Coronary heart disease	5 (31.3)	1 (4.8)	0.082
Chronic kidney disease	1 (6.3)	3 (14.2)	0.297
Valvular heart disease	1 (6.3)	0 (0)	1.000
Hx of Stroke	4 (25.0)	1 (4.8)	0.157
Other	4 (25.0)	4 (19.0)	1.000
Medication	12 (48.0)	14 (56.0)	0.571
Aspirin	9 (75.0)	3 (21.4)	0.047
Warfarin	1 (8.3)	0 (0)	1.000
Statin	10 (83.3)	4 (28.9)	0.059
ACEI/ARB	2 (16.7)	4 (28.9)	0.384
Beta-blocker	2 (16.7)	2 (14.3)	1.000
CCB	3 (25.0)	4 (28.9)	0.462
Other	7 (58.3)	11 (78.6)	0.239
Severity COVID-19			0.481
Roon Air	19 (76)	15 (60.0)	
Oxygen cannula	2 (8.0)	6 (24.0)	
Oxygen mask with bag	0 (0.0)	0 (0.0)	
Oxygen High Flow	2 (8.0)	2 (8.0)	
Endotracheal tube with ventilator	2 (8.0)	2 (8.0)	

Table 1 Demographic data of COVID-19 patients (n = 50) (cont.)

Demographic	Stroke patient (n = 25)	Non-Stroke patient (n = 25)	p-value
Vital Sign			
Body temperature (^{o} c)	36.93±0.77	37.17±0.86	0.309
Pulse (bpm)	88.32±10.41	86.86±14.32	0.690
Respiratory rate (/min)	20.48±2.73	20.09±0.27	0.600
Systolic blood pressure (mmhg)	150.28±30.91	134.23±23.04	0.052
Diastolic blood pressure (mmhg)	86.56±16.98	74.41±12.34	0.008*
Oxygen saturation (% at room air)	96.65±5.25	96.42±3.32	0.851

Value is represented as number (%), Mean±SD, * significance at p<0.05

Table 2 Laboratory testing of Covid-19 patients (n = 50)

Laboratory	Stroke patient (n = 25)	Non-Stroke patient (n = 25)	p-value
D-Dimer (mg/l)	4.64±6.95	2.56±8.00	0.334
hs-CRP (mg/dL)	3.26±4.18	4.38±5.62	0.431
Fasting blood sugar(mg/dL)	122.33±42.39	155.04±69.83	0.134
HbA1C(%)	6.46±2.01	8.30±3.22	0.100
HDL(mg/dL)	40.27±14.93	40.00±0.00	0.986
LDL(mg/dL)	116.55±42.29	69.00±0.00	0.284
Cholesterol(mg/dL)	183.18±47.25	131.00±0.00	0.292
Triglyceride(mg/dL)	138.71±77.24	82.00±0.00	0.484
Sodium (mEq/L)	138.71±3.93	135.12±6.13	0.019
Potassium(mEq/L)	3.85±0.39	3.86±0.40	0.870
BUN (mg/dL)	17.13±18.36	21.93±20.33	0.385
Cr (mg/dL)	2.94±8.09	1.25±1.33	0.310
eGFR (ml/min/1.73m²)	74.12±28.38	76.32±28.27	0.785
Hb (g/dl)	11.59±2.09	12.23±2.47	0.338
Hct (%)	35.81±6.17	36.64±7.30	0.670
WBC (x10^{3}cells/cu.mm.)	8.63±3.18	7.99±3.88	0.530
Neutrophil(%)	65.77±13.39	70.59±16.31	0.271
Lymphocyte(%)	22.45±12.01	18.30±11.56	0.279
Monocyte(%)	6.45±2.94	7.78±6.26	0.390
Eosinophil(%)	4.11±4.24	1.17±1.46	0.127
Platelet (x10^{3}cells/cu.mm.)	263.08±93.224	25.276±121.529	0.738

Table 3 Factors associated with stroke.

Factors	Crude OR	p-value	Adjusted OR	p-value
DBP	0.95(0.9-0.98)	0.015*	0.93(0.88-0.98)	0.008*
Antiplatelet use	0.24(0.06-1.04)	0.047*	0.18(0.03-0.97)	0.046

Table 4. Stroke patients' Characteristics (n = 25)

Characteristics	n (%)
Toast	
Lacunar stroke	14(56.0)
Large vessel atherosclerosis	4(25.0)
Cryptogenic stroke	4(25.0)
Cardioembolic	3(12.0)
NIHSS	6.96$\pm$5.12
Mild	10(40.0)
Moderate	12(48.0)
Moderate to severe	3(12.0)

Discussion

This study investigated the correlation of elevated D-Dimer levels in acute ischemic stroke in COVID-19 patients. The study included 50 COVID-19 patients, with 25 of them having acute ischemic stroke and 25 without. The study population was mostly male, with no statistically significant differences in age, BMI, underlying disease and COVID-19 severity among the two groups. The only statistically significant difference in vital signs at admission was diastolic blood pressure, with an increase in diastolic blood pressure by 1 mmHg resulting in a 7% decrease in the risk of ischemic stroke (p=0.01). This study suggests that diastolic blood pressure may be a predictor of ischemic stroke in COVID-19 patients.

The study found that COVID-19 patients with acute ischemic stroke had no significantly higher D-Dimer levels (4.64±6.95) compared to the general COVID-19 population (2.56±8.00) (p=0.334). However, no other laboratory values were found to be significantly different between the two groups. The study identified two protective factors for ischemic stroke in COVID-19 patients: increased diastolic blood pressure (p=0.008) and usage of antiplatelet medications (p=0.046). These findings suggest that diastolic blood pressure and antiplatelet medication usage may be protective factors against ischemic stroke in Covid-19 patients.

This study suggests that D-Dimer may not be associated with acute ischemic stroke in COVID-19 patients. This is in line with literature reviews that indicate multiple mechanisms for acute ischemic stroke and D-Dimer is recorded as a spot diagnosis at diagnosis. However, D-Dimer can also be caused by several conditions other than acute ischemic stroke, thus D-Dimer levels may not be a reliable indicator of acute ischemic stroke in COVID-19 patients.

This statement suggests that the incidence of acute ischemic stroke in COVID-19 patients at Rajavithi hospital in Thailand is lower than the incidents reported in China and the United States. However, it is important to note that this comparison may not be entirely accurate due to differences in population demographics, healthcare systems, and other factors. Additionally, the data is only specific to Rajavithi hospital and may not be reflective of the situation in other parts of Thailand.

These limitations suggest that the study may not have had enough participants to draw definitive conclusions, and that the short duration of treatment and observation may not have allowed for enough

time to observe the full effects of the treatment. Additionally, the fact that COVID-19 is a new disease means that there is limited knowledge about its effects on the human body, which may impact the accuracy of the study's findings.

Conclusion

This study suggests that there is no significant relationship between high D-dimer levels and ischemic stroke events in COVID-19 patients. However, the study's conclusions may be limited by the small sample size and short duration of observation and follow-up. Further research with larger study populations and longer observation periods is needed to confirm these findings.

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