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Research Paper

# Risk Factors of Ischemic Stroke in COVID-19 Patients

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## ABSTRACT:

**BACKGROUND:**

The Coronavirus Disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), has become one of the worst pandemics in this century. COVID-19 may increase the risk of acute ischemic stroke similar to the increased risk of 3.2-fold to 7.8-fold seen within the first 3 days after other respiratory tract infections.

**OBJECTIVE:**

To have the ability of predicting risk of stroke development in COVID 19 patients by relaying on variable parameters involving clinical and inflammatory markers.

**METHODS AND MATERIALS:**

A case control study conducted in Baghdad, the capital of Iraq at Baghdad teaching Hospital, in a period from March 2021 till August 2021.the study included 90 patients tested positive for COVID-19 infection.

**RESULTS:**

The mean age of participants was 58.2 ± 15.6 years (range 22 – 88 years old). The mean age across group A was 65.4 years which was significantly higher than group B age (p=0.0001). Regarding gender, males were representing 53% and 46% of group A and B respectively. Regarding the severity, no mild cases was observed among group A patients (p=0.001). Regarding risk factors, hypertension, DM, history of CVD, smoking, and were associated significantly with developing ischemic stroke (p<0.05). Also, developing respiratory failure was associated with development of ischemic stroke (p=0.002). Regarding inflammatory markers, D-Dimer and ferritin levels were significantly higher among group A patients in comparison to group B patients (p<0.05). While, LDH did not demonstrated significant difference between both groups (p=0.14).

**CONCLUSION:**

Age, hypertension, D.M, smoking, Hx of CVD, Severity of COVID-19 infection, respiratory failure and D-Dimer, ferritin levels were significantly higher among COVID patients who developed stroke. LDH did not demonstrated significant difference.


**KEYWORDS**: Ischemic stroke,COVID-19 ,D-dimer,Ferritin,Immune mechanism

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## INTRODUCTION:

The Coronavirus Disease 2019 (COVID-19), which regarded as one of the worst pandemics in this century is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) announced that COVID-19 had become a pandemic on March 11th, 2020.(1)

COVID-19 can increase the risk of acute ischemic stroke(2) just similar to the increased risk of 3.2-fold to 7.8-fold that had been observed within the first 3 days after other respiratory tract infections.(3,4)In a review of literature in April 2020,(5) the percentage of stroke was 4.9% of COVID-19 patients during initial hospitalization especially those with severe infection. (6,7,8,9)

The increased risk of ischemic stroke most probably multifactorial, with activation of inflammatory and coagulation pathways reflected by increased d-dimer levels, CRP, lactic acid dehydrogenase, and WBC count.(10, 11)

Reports from China reveal a high incidence of neurological manifestations, with estimated 36% of COVID-19 patients experiencing neurological symptoms 5.7% of severe disease had developed acute cerebrovascular disease compared with 0.8% of patients with non-severe disease.(12,13)

Multiple factors had been attributed to stroke development rather than a single pathway and key proposed mechanisms include the development of cytokine storm and activation of the innate immune system, embolic events propagated by hypoxia-induced ischemia secondary to severe pulmonary disease, thrombotic microangiopathy, endotheliopathy/ endothelialitis, pre- existing or new-onset arrhythmias and multifactorial activation of coagulation.

The one unifying factor that seems to increase the risk of acute ischemic stroke in COVID-19 patients is the elevated levels of D-Dimer.[14]

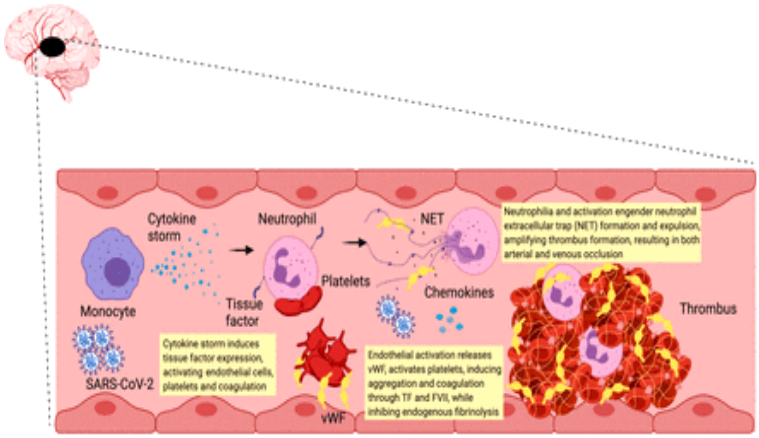


**Figure 1: Summary of COVID-19-associated coagulopathy (CAC).**

## PATIENTS AND METHOD:

A Case Control study was conducted in Baghdad, the capital of Iraq at Medical city Baghdad teaching hospital, in a period from March 2021 till August 2021.

**Inclusion and Exclusion Criteria**

The study population involved all patients *who met the following criteria:*

1. Adult patients > 18 years old.
2. Who diagnosed with COVID-19 by PCR test+/- CT chest
3. Have stroke after COVID-19 infection

*Exclusion criteria:*

1. Patients with post COVID-19 ICH, SAH or CVT.
2. Critically ill patients

**Viral Detection:** COVID19 diagnosis was confirmed by PCR of nasopharyngeal specimens.

**Tool of data collection**

Data collected by direct interview with all respondents, the interview is done by a questionnaire which comprises two parts:

**Part One:** Which includes questions regarding demographic data:

Age, Gender, Medical history of other disease, Smoking status: previously or currently smoking and Duration since COVID-19 infection and development of stroke.

**Part Two:**

Lab investigation, which included:

WBC, D-Dimer, Ferritin level, LDH and CRP

## RESULTS:

There were 90 COVID-19 have been included in this study which divided for 2 groups, group A (45 patients), included patients who developed Ischemic stroke after COVID-19 and group B (45 patients), included patients who did not develop Ischemic stroke.

**Demographic characteristics**

The mean age of participants was 58.2 ± 15.6 years (range 22 – 88 years old). The mean age across group A was 65.4 years which was significantly higher than group B age (p=0.0001) (Table 1).

**Table 1:Group Statistics comparison between groups for Age.**

| | Case | N | Mean | Std. Deviation | P value* |
|---|---|---|---|---|---|
| Age | Case | 45 | 65.4 | 10.51 | 0.0001 |
| | Control | 45 | 51.1 | 16.79 | |

***Independent sample t test***

Regarding gender, males were representing 53% and 46% of group A and B respectively. No significant difference has been observe between both group (p=0.52) (Table 2).

**Table 2: Sex distribution across groups.**

| | | | Case | | Total |
|---|---|---|---|---|---|
| | | | Case | Control | |
| Sex | Female | Count | 20 | 23 | 43 |
| | | % within Sex | 46.5% | 53.5% | 100.0% |
| | Male | Count | 25 | 22 | 47 |
| | | % within Sex | 53.2% | 46.8% | 100.0% |
| Total | | Count | 45 | 45 | 90 |
| | | % within Sex | 50.0% | 50.0% | 100.0% |

***Chi-Square=0.4, P=0.52***

Regarding the severity, no mild cases was observed among group A patients and there was significant difference between group A and b regarding the severity in which the severity was associated with development of ischemic stroke (p=0.001) (Table 3).

**Table 3: Severity distribution across patients' groups.**

| | | | Case | | Total |
|---|---|---|---|---|---|
| | | | Case | Control | |
| **Severity** | **Mild** | Count | 0 | 16 | 16 |
| | | % within Severity | 0.0% | 100.0% | 100.0% |
| | **moderate** | Count | 28 | 21 | 49 |
| | | % within Severity | 57.1% | 42.9% | 100.0% |
| | **Sever** | Count | 17 | 8 | 25 |
| | | % within Severity | 68.0% | 32.0% | 100.0% |
| **Total** | | Count | 45 | 45 | 90 |
| | | % within Severity | 50.0% | 50.0% | 100.0% |

***Chi-Square=20.2, P=0.001***

Regarding risk factors, hypertension, DM, history of CVD, smoking, and obesity were associated significantly with developing ischemic stroke (p<0.05). Also, developing respiratory failure was associated with development of ischemic stroke (p=0.002) (Table 4).

**Table 3: Severity distribution across patients' groups.**

| | | Case | | Control | | P value* |
|---|---|---|---|---|---|---|
| | | Count | Row N % | Count | Row N % | |
| HTN | No | 6 | 21.4% | 22 | 78.6% | **0.0001** |
| | Yes | 39 | 62.9% | 23 | 37.1% | |
| DM | No | 12 | 27.3% | 32 | 72.7% | **0.0001** |
| | Yes | 33 | 71.7% | 13 | 28.3% | |
| CVD | No | 29 | 40.8% | 42 | 59.2% | **0.001** |
| | Yes | 16 | 84.2% | 3 | 15.8% | |
| Smoking | No | 30 | 40.0% | 45 | 60.0% | **0.001** |
| | Yes | 15 | 100.0% | 0 | 0.0% | |
| Obesity | No | 39 | 46.4% | 45 | 53.6% | **0.01** |
| | Yes | 6 | 100.0% | 0 | 0.0% | |
| Respiratory failure | No | 27 | 40.3% | 40 | 59.7% | **0.002** |
| | Yes | 18 | 78.3% | 5 | 21.7% | |

****Chi-Square test and exact Fisher's test***

Regarding WBC, the mean WBC count was not differ significantly between group A and B (p=0.62) (Table 5).

**Table 5: Group Statistics comparison between groups for WBC.**

| | Case | N | Mean | Std. Deviation | P value* |
|---|---|---|---|---|---|
| WBC | Case | 45 | 12.79 | 4.94 | 0.62 |
| | Control | 45 | 12.27 | 4.95 | |

Regarding inflammatory markers, D-Dimer and ferritin levels were significantly higher among group A patients in comparison to group B patients ($p<0.05$). While, LDH did not demonstrated significant difference between both groups ($p=0.14$) (Table 6).

**Table 6: Group Statistics comparison between groups for LDH, D-Dimer, and Ferritin.**

| | Case | N | Mean | Std. Deviation | P value* |
|---|---|---|---|---|---|
| LDH | Case | 45 | 393.3 | 261.4 | 0.14 |
| | Control | 45 | 320.2 | 202.5 | |
| D-Dimer | Case | 45 | 2001.1 | 4783.6 | **0.02** |
| | Control | 45 | 326.8 | 1510.1 | |
| Ferritin | Case | 45 | 679.4 | 554.6 | **0.01** |
| | Control | 45 | 332.5 | 259.6 | |

***Independent sample t test***

The correlation between age and inflammatory markers across all patients, all parameters showed significant positive weak correlation with age (Table 7).

**Table 7: Correlations analysis between age and inflammatory markers across.**

| | | Age | LDH | D-Dimer | Ferritin |
|---|---|---|---|---|---|
| Age | Pearson Correlation | 1 | 0.256 | 0.271 | 0.385 |
| | P value | | **0.015** | **0.010** | **0.001** |
| | N | 90 | 90 | 90 | 90 |

The mean duration of for developing ischemic stroke after COVID-19 was 2.29 ± 3.3 weeks (range 1 – 14 weeks).

**Table 8: Binary logistic regression analysis for group A and B with studied factors**

| | | Score | df | P value |
|---|---|---|---|---|
| Variables | Sex | 0.4 | 1 | 0.527 |
| | Severity | 20.2 | 2 | **0.0001** |
| | HTN | 13.2 | 1 | **0.0001** |
| | DM | 17.7 | 1 | **0.0001** |
| | CVD | 11.2 | 1 | **0.001** |
| | Smoking | 18.0 | 1 | **0.0001** |
| | Obesity | 6.4 | 1 | **0.011** |
| | Respiratory Failure | 9.8 | 1 | **0.002** |
| | LDH | 2.1 | 1 | 0.13 |
| | D-Dimer | 4.8 | 1 | **0.028** |
| | Ferritin | 12.6 | 1 | **0.001** |
| Overall Statistics | | 46.753 | 9 | **0.0001** |

Binary logistic regression analysis for group A and B with studied factors showed, keeping all other variables constant, being having sever COVID, having hypertension, having DM, having history of previous CVD, being smoker, being obese, and developing respiratory failure during COVID-19 infection showed significant association with developing ischemic stroke after COVID-19. Also, higher D-Dimer level and higher Ferritin level were associated with developing ischemic stroke, by keeping all other variables constant (Table 8).

## DISCUSSION:

COVID-19 is associated with inflammatory coagulopathy that causes various multiple vascular obstructions, including acute ischemic stroke.[15]

Our aim is to evaluate risk factors that contribute to stroke in COVID-19 patients.

The mean age across cases was 65.4 years which was significantly higher than control group. This was in line with other studies that showed a significant difference in age between COVID-19 patients who develop ischemic stroke, in which the mean age was 68 years.[16]

It has been understood that stroke incidence is higher in men than in women globally. However, in this study, we found that ischemic stroke caused by COVID-19 did not differ significantly between genders. This was in line with other studies that showed no significant difference between gender in COVID-19 patients who develop ischemic stroke and those who did not [24-27].

Regarding the severity, no mild cases were observed among cases patients and there was significant difference between cases and control regarding the severity in which the severity was associated with development of ischemic stroke. This was in line with Li et al study that showed the ischemic stroke more likely to present with severe COVID-19 infection.[25]

Regarding risk factors, hypertension, DM, history of CVD, and smoking were associated significantly with developing ischemic stroke ($p<0.05$). Also, developing respiratory failure was associated with development of ischemic stroke. While other studies have reported findings similar to our findings[17, 18,19] suggesting that even if COVID-19 was a predisposing factor, the risk was mainly seen in those who were already at risk for acute ischemic stroke due to other cardiovascular risk factors.

Regarding WBC, the mean WBC count does not differ significantly between groups, which differ from a study reported by Zhang et al showed that there was significant higher WBC count among stroke COVID- 19 patients and this could be relate to sample size difference.[28]

Regarding inflammatory markers, D-Dimer and S.ferritin levels were significantly higher among cases patients in comparison to control patients, while, LDH did not demonstrated significant difference between both groups.

High level of D-Dimer associated with higher mortality rate and COVID-19 virus increase its level significantly[21,22,23,24,25] .

A ferritin level, too, was significantly higher among cases patients in comparison to control patients. In fact, ferritin level was associated with severe cases of COVID-19 patients.

LDH did not demonstrated significant difference between both groups. And this was against study conducted Karvigh et al that showed a significant increase in LDH in patients with COVID-19 and ischemic stroke.[29] The difference between our study and other studies might relate to sample size and study designation difference.

## CONCLUSION:

Based on study results, we concluded the following:

1. The age among COVID patients who developed stroke was significantly higher in comparison to COVID patients who did not develop stroke.
2. Severity of illness was associated with development of ischemic stroke among COVID patients.
3. Regarding risk factors, hypertension, DM, history of CVD and smoking were associated significantly with developing ischemic stroke.
4. D-Dimer and ferritin levels were significantly higher among COVID patients who developed stroke compared to those who do not.
5. LDH did not demonstrated significant difference between COVID patients who developed did not develop stroke.

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