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COVID-19 independently predicts poor outcomes in Acute Ischemic Stroke- Insights from a multicenter study from Pakistan and United Arab Emirates

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Background: Ischemic stroke associated with coronavirus 2019 (COVID-19) has been well recognized by now. Few studies have compared COVID related versus unrelated strokes. We intend to report on a large group of Asian patients from two countries and compare COVID with non-COVID strokes admitted during the same time period.

Methods: Consecutive cases of acute ischemic stroke either presenting or developing, between March 2020 and December 2021 in four tertiary care hospitals (1 in Dubai, UAE and 3 in Karachi, Pakistan) and testing positive for COVID-19 were included in the study. Patients admitted with ischemic stroke during the same time period and who tested negative for COVID-19 were also randomly selected from the four hospitals. All data was collected from the medical records of the patients and recorded on a standard questionnaire before it was entered in SPSS version 21 for analysis.

Results: There were 139 COVID positive and 271 COVID negative patients with acute ischemic stroke included in the current study. There were significantly more males (80.6% vs 64.9%, p=0.001) and more large vessel strokes in the COVID positive group (41% vs 21.8%, p < 0.001). Being COVID positive was an independent predictor of poor outcome at discharge, defined as a modified Rankin score of 3-6 (OR 3.87, 95% CI 2.21-6.77) after adjusting for country, age, sex, vascular comorbid conditions and stroke subtype. Conclusions: In this largest series of patients with COVID related strokes from Asia, COVID-19 was an independent predictor of poor outcomes at discharge after adjusting for other variables.

Keywords: COVID-19—Ischemic stroke—Functional outcomes—Mortality

Introduction

Since the first appearance of Corona virus disease 2019 (COVID-19), new insights into various clinical presentations are coming to light. What started off as an acute respiratory illness, is now known to have wider effects, including the cardiovascular and cerebrovascular systems. Neurological complications 3, and in particular ischemic strokes 2-4, have been reported in multiple publications. Few studies however, have compared COVID and non-COVID ischemic strokes 5,6, and even fewer have looked at how it impacts outcomes of strokes.

The objective of our study is to report ischemic strokes in COVID-19 positive patients from four centers from two Asian countries and compare with non-COVID ischemic strokes from the same time period in order to understand differences in risk factors and outcomes.

Methods

The study was carried out in three centers in Karachi, Pakistan and one center in Dubai, United Arab Emirates. All four centers are tertiary care hospitals that routinely...
admit stroke patients. Consecutive patients admitted between March 1st, 2020 and December 31st, 2021 with acute ischemic stroke and who tested positive for COVID-19 at the time of stroke admission were included as cases. From all non-COVID acute ischemic stroke admissions during this time period, a random sample of 280 patients was taken as controls, to achieve a case to control ratio of 1:2. Non COVID status was defined as a negative PCR at admission and no symptoms and signs suggestive of COVID during the admission. In order to ensure proper representation, non-COVID strokes were selected from the same centers as COVID-strokes, two controls for every case selected. This was done retrospectively, all non-COVID stroke patients admitted during the study period at a center were assigned unique IDs and entered into a database on SPSS, from where a random list was generated for the required number of cases from that center. After accounting for missing data, 139 COVID positive and 271 COVID negative patients were included in the current analysis.

Data was extracted from medical records on a pre-designed standard questionnaire. The following information was gathered, basic demographic characteristics, vascular risk factors, radiological findings, stroke etiology based on TOAST classification, treatment received in hospital and at discharge and outcomes. For COVID positive patients, additional information with regard to diagnosis and severity of their COVID was also collected.

The data was entered into Statistical Program for Social Sciences, SPSS version 21 for analysis.

**Statistical analysis**

Means and standard deviation were calculated for continuous variables, and frequencies are reported for categorical variables. Independent sample t-test was used to compare continuous variables between COVID and non-COVID positive patients and chi-square test of independence was used to compare categorical variables. Binary logistic regression was used to model predictors of outcome at discharge. $P<0.05$ was taken as significant.

**Ethical approval**

Respective Institutional Review Boards reviewed and approved the protocol at each of the participating centers.

| Table 1. Characteristics of COVID19 patients. |
|---------------------------------------------|
|                                             |
| **Total (139)** | **UAE (70)** | **Pakistan (69)** | **P value** |
|-----------------|--------------|-------------------|-------------|
| **Age years Mean(SD)** | 58.24 (15.21) | 51.5 (13.97) | 65 (13.4) | <0.001 |
| **Male** | 112 (80.6) | 65 (92.9) | 47 (68.1) | <0.001 |
| **Comorbid conditions** | | | | |
| Diabetes | 78(56.1) | 34(48.6) | 44 (63.8) | <0.051 |
| Hypertension | 95(68.3) | 38(54.3) | 57(82.6) | <0.001 |
| Dyslipidaemia | 30(20.6) | 18(25.7) | 12(17.4) | <0.162 |
| Ischemic Heart Disease | 25(18) | 8(11.4) | 17(24.6) | <0.035 |
| Prior stroke | 19(13.7) | 1(1.4) | 18(26.1) | <0.001 |
| Abnormal Chest Xray | 84(60.4) | 30 (42.9) | 54 (80.6) | <0.001 |
| **Symptoms** | | | | |
| Fever | 59 (42.4) | 18 (26.1) | 41 (59.4) | <0.001 |
| Cough | 48 (34.5) | 18 (5.7) | 30 (43.5) | 0.03 |
| Shortness of breath | 44 (31.7) | 7 (10.0) | 37 (53.6) | <0.001 |
| Headache | 7 (5.0) | 7 (10) | 0 (0) | NA* |
| Myalgi | 5 (4.3) | 5 (7.1) | 0 (0) | NA* |
| Diarrhoea | 5 (3.6) | 4 (5.7) | 1 (1.4) | NA* |
| Rhinorrhea | 2 (1.4) | 2 (2.9) | 0 (0) | NA* |
| Loss of taste & smell | 2 (1.4) | 0 (0) | 2 (2.9) | NA* |
| **Duration of symptoms before stroke days Mean (SD)** | | | | |
| TOAST | 6.31 (7.04) | 5.90 (5.89) | 7.04 (8.79) | 0.50 |
| Large artery | 57(41) | 12(17.1) | 45 (65.2) | |
| Small vessel | 11(7.9) | 7(10) | 4(5.8) | |
| Cardioembolic | 18(12.9) | 8(11.4) | 10(14.5) | <0.001 |
| Other determined | 21(15.1) | 11(15.7) | 10(14.5) | |
| Undetermined | 32(33) | 32(45.7) | 0 | |
| mRS 3-5 | 85(77.3) | 34(63) | 51(91.1) | <0.001 |
| Mortality | 28(20.3) | 16(22.9) | 12(17.6) | 0.292 |

Numbers are frequency (percentage) unless otherwise indicated.

* condition for Chi square is not met.
Results

A total of 139 COVID positive patients were included in the current analysis, seventy from UAE and 69 from Pakistan. The mean age of patients with COVID-19 associated stroke was 58.24 (SD 15.21) years and 80.6% were males. COVID-19 diagnosis was based on clinical symptoms and was confirmed with PCR for nasopharyngeal swab in 83.5% patients, and by antibodies in 12.9%. A small proportion had other methods of confirmation (PCR for saliva etc). Chest X-ray was abnormal in 60.4%. Fever, followed by cough and shortness of breath were the commonest symptoms. A minority of patients presented within the window for intervention, seven of them underwent thrombolysis and two had mechanical thrombectomy.

The patients from Pakistan were older (65 years vs 51.5 years, p < 0.001), and the proportion of males was lower compared to UAE (68.1% vs 92.9%, p < 0.001). The patients from Pakistan were also more likely to have vascular comorbid conditions like hypertension, ischemic heart disease, and prior stroke, and stroke etiology was also more frequently found to be large artery atherosclerosis. Also, the symptoms of cough, shortness of breath and fever were also more commonly seen in Pakistani patients, whereas those from UAE had milder symptoms of headache, myalgia and diarrhea. In the univariate analysis, the outcomes of patients from Pakistan was also significantly worse with 91% having modified Rankin Score of 3-5 at discharge. This comparison is presented in Table 1.

Table 2 shows the comparison between COVID positive and COVID negative stroke cases. There was no significant difference in age (58.24 vs 58.15, p=0.95) between the two groups. However, COVID positive stroke patients were more frequently males (80.6 vs 64.9%, p=0.001) and more frequently diabetic (56.1% vs 43.9%, p=0.02). There were no significant differences in the other comorbid conditions. The location of infarction did not differ between COVID and non-COVID strokes, but those with COVID

| Table 2. Demographic and clinical features of COVID and non-COVID related strokes. |
|------------------------------------------|-----------------|-------------------|
| COVID Positive (139) | COVID Negative (271) | P value |
| Age years Mean (SD) | 58.24 (15.2) | 58.15 (13.7) | 0.95 |
| Males | 112 (80.6) | 176 (64.9) | 0.001 |
| Comorbid Conditions | | | |
| Diabetes | 78 (56.1) | 119 (43.9) | 0.022 |
| Hypertension | 95 (68.3) | 186 (68.6) | 1.0 |
| Dyslipidemia | 30 (21.6) | 39 (14.4) | 0.07 |
| Atrial Fibrillation | 6 (4.3) | 16 (5.9) | 0.65 |
| Prior Stroke | 19 (13.7) | 37 (13.7) | 1.0 |
| Ischemic Heart Disease | 25 (18%) | 32 (11.8) | 0.1 |
| Infarct Location | | | |
| Cortical | 88 (63.3) | 149 (55) | 0.11 |
| Subcortical | 43 (30.9) | 82 (30.3) | 0.9 |
| Brainstem | 11 (7.9) | 32 (11.8) | 0.24 |
| Cerebellum | 20 (14.4) | 24 (8.9) | 0.09 |
| Hemorrhagic Transformation | 31 (22.3) | 2 (0.7) | <0.001 |
| Multiple vascular territory | 28 (20.1) | 25 (9.2) | 0.002 |
| Anterior circulation | 90 (64.7) | 186 (68.6) | 0.522 |
| Thrombus on Vascular imaging | 11 (12.6) | 12 (4.8) | 0.019 |
| Acute treatment (IVTPA) | 7 (5) | 17 (6.3) | 0.369 |
| Anticoagulation with LMWH/heparin | 8 (5.8) | 7 (2.6) | <0.001 |
| Anticoagulation at discharge | 4 (3.3) | 2 (0.7) | <0.001 |
| TOAST classification | | | |
| Large artery | 57 (41) | 59 (21.8) | <0.001 |
| Small vessel | 11(7.9) | 78(28.8) | |
| Cardioembolic | 18(12.9) | 49(18.1) | |
| Other determined | 21(15.1) | 24(8.9) | |
| Undetermined | 32(23) | 61(22.5) | |
| Modified Rankin Score at Discharge | | | |
| 0-2 | 26 (18.7) | 131 (48.3) | <0.001 |
| 3-5 | 85 (61.2) | 137 (50.6) | |
| 6 | 28 (20.1) | 3 (1.1) | |

Numbers are frequency (percentage) unless otherwise indicated.
related strokes were more likely to have multiple vascular territories involved and to have hemorrhagic transformation of their ischemic strokes. The latter may be related to a greater use of anticoagulation in COVID related strokes (5.8% vs 2.6%, p<0.001). Rate of thrombolysis was not significantly different in COVID positive vs COVID negative patients (5% vs 6.3%, p=0.37).

Etiological classification of COVID and non-COVID strokes also differed significantly. Large artery atherosclerosis was the cause in 41% of COVID related strokes in comparison to 21.8% of non-COVID strokes. Small vessel disease was much less likely in COVID related cases (7.9% vs 28.8%, p<0.001) (Fig. 1).

The outcomes at discharge were significantly worse for COVID positive patients. 77.3% were moderately disabled at discharge compared to 51.3% of non-COVID strokes. Mortality was also significantly higher in COVID positive stroke patients (20.3% vs 1.1%, p<0.001). Table 2 summarizes these comparisons.

Binary logistic regression was carried out to look for predictors of poor functional outcome (defined as mRS of 3-5). After adjusting for country, age, sex, comorbid conditions (Diabetes, hypertension, dyslipidemia, atrial fibrillation, ischemic heart disease and prior stroke), location and etiology of stroke, stroke patients with COVID-19 were at 3.87 times higher odds of poor functional outcome at discharge (defined as mRS of 3-5 or mortality) (Table 3). It was also a significant predictor of inpatient mortality when modeled separately for this outcome.

We ran separate models for patients from Pakistan and UAE to evaluate if the strength of the association varies between the two populations. We found COVID-19 status to independently predict poor outcomes after adjusting for age, sex, comorbid conditions, location and stroke

![Fig. 1. Comparison of proportions of Ischemic Stroke subtypes between COVID and non-COVID strokes.](image)

| Variables in the model                          | OR     | 95% CI          | P-value |
|------------------------------------------------|--------|-----------------|---------|
| COVID-19 positive                              | 4.07   | 2.50-6.63       | <0.001  |
| Adjusted for Country                           |        |                 |         |
| COVID-19 positive                              | 4.29   | 2.60-7.06       | <0.001  |
| Adjusted for Age and Sex                       |        |                 |         |
| COVID-19 positive                              | 4.46   | 2.68-7.41       | <0.001  |
| Adjusted for Age, sex, and vascular comorbid*  |        |                 |         |
| COVID-19 positive                              | 4.38   | 2.57-7.46       | <0.001  |
| Adjusted for Age, sex, vascular comorbid*, and location of stroke** |        |                 |         |
| COVID-19 positive                              | 3.87   | 2.21-6.77       | <0.001  |
| Adjusted for Age, sex, vascular comorbid, location of stroke and TOAST classification*** |        |                 |         |

*Vascular comorbid include Diabetes, Hypertension, Dyslipidemia, Atrial fibrillation, Ischemic heart disease, and prior stroke.
**Location of stroke includes cortical, subcortical, brainstem and cerebellum.
***TOAST classification includes large artery atherosclerosis, small vessel disease, cardioembolic, other determined and undetermined.
etiology, although the strength of association was much stronger for patients from Pakistan (Table 4).

Discussion

We report the largest series from Asia of acute ischemic stroke in COVID-19 patients and the comparison with non-COVID strokes during the same time period. Our results highlight differences in stroke etiologies between the two groups despite similar risk profiles, as well as poor outcomes in patients with COVID-19. Although patients from UAE were younger and had fewer comorbid conditions compared to those from Pakistan, poor outcomes associated with COVID-19 were independent of these differences.

When COVID positive stroke patients were compared with COVID negative patients, no significant differences were observed in terms of age. However, there were significantly more males amongst the COVID positive stroke patients. This is in line with reports from other studies and a recent review that has looked at 455 ischemic stroke patients reported in literature.

Vascular co-morbid conditions were not significantly different between the two groups, except for a greater proportion of diabetics in the COVID positive cohort (56.1% vs 43.9%, p=0.02), a finding earlier reported in a meta-analysis by Katsanos et al. Several other studies have found a high prevalence of diabetes, hypertension and atrial fibrillation in patients with COVID related strokes. Vascular co-morbid conditions were not significantly different between the two groups, except for a greater proportion of diabetics in the COVID positive cohort (56.1% vs 43.9%, p=0.02), a finding earlier reported in a meta-analysis by Katsanos et al 10. Several other studies have found a high prevalence of diabetes, hypertension and atrial fibrillation in patients with COVID related strokes 11,12.

The other significant difference was observed in involvement of multiple vascular territories consistent with an earlier report and hemorrhagic transformation, which were both more significantly found in COVID positive strokes. The former may be attributable to the underlying mechanism of hypercoagulability, as earlier reported 14. The latter may be secondary to an increased use of anticoagulation in COVID positive patients.

Stroke etiologies were also more likely to be large artery disease in COVID positive patients with a significantly higher proportion having thrombus identified on vascular imaging compared to non-COVID strokes. This may be reflective of the underlying mechanisms leading to COVID related strokes 15,16. The etiological diagnoses reported in literature are variable, but most studies found cryptogenic strokes followed by large artery etiology as the predominant stroke type in COVID positive stroke patients. We found small vessel disease as the commonest etiology in non-COVID strokes whereas only a mere 7.9% of COVID related strokes were of this etiology. This finding is reported earlier as well and is further confirmation for the underlying mechanisms leading to COVID related strokes.

A higher in hospital mortality and poor functional outcome is reported in COVID related strokes in an earlier study from India where 21% died and 59.7% had mRS at 3-5 and from France where 60% of COVID related stroke patients had mRS 3-6 at discharge. Another study from Qatar reported poor functional outcomes (mRS 3-6) in 71.9% of their COVID stroke patients. A systematic review reporting on 899 COVID related strokes, reported a mortality of 31.8%. Our study showed a mortality of 20.3% and mRS 3-5 in 61.2% of COVID related strokes.

We also showed that after adjusting for other variables like age, sex, vascular risk factors and stroke etiology, COVID-19 remained an independent predictor of poor outcomes in stroke patients including mortality. A study from Spain found COVID-19 to be an independent predictor of mortality but not of poor functional outcomes but these outcomes were determined at 3 months. The global COVID 19 stroke registry had findings similar to ours where patients with COVID-19 had higher risk of severe disability and death at discharge.

Although it was not our intention to compare patients from UAE and Pakistan, some important differences we

### Table 4. Logistic regression model: COVID19 as predictor of poor functional outcome (mRS 3-6) in cases from UAE and Pakistan analyzed separately.

| Variables in the model | UAE OR (95%CI) | PAKISTAN OR (95% CI) |
|------------------------|---------------|---------------------|
| COVID-19 positive      | 2.17 (1.17-4.01) | 10.66 (4.31-26.35) |
| COVID-19 positive      | 2.45 (1.29-4.66) | 10.35 (4.16-25.71) |
| Adjusted for Age and Sex | 2.54 (1.31-4.93) | 11.21 (4.36-28.83) |
| COVID-19 positive      | 2.60 (1.27-5.33) | 9.22 (3.52-24.13)  |
| Adjusted for Age, sex, vascular comorbid* | 2.40 (1.09-5.27) | 8.17 (3.05-21.90)  |
| COVID-19 positive      | 2.45 (1.29-4.66) | 10.35 (4.16-25.71) |
| Adjusted for Age, sex, vascular comorbid*, and location of stroke** | 2.54 (1.31-4.93) | 11.21 (4.36-28.83) |
| COVID-19 positive      | 2.60 (1.27-5.33) | 9.22 (3.52-24.13)  |
| Adjusted for Age, sex, vascular comorbid, location of stroke and TOAST classification*** | 2.40 (1.09-5.27) | 8.17 (3.05-21.90)  |

*Vascular comorbid include Diabetes, Hypertension, Dyslipidemia, Atrial fibrillation, Ischemic heart disease, and prior stroke.
**Location of stroke includes cortical, subcortical, brainstem and cerebellum.
***TOAST classification includes large artery atherosclerosis, small vessel disease, cardioembolic, other determined and undetermined.
noted were a significantly younger age and more males in the patients from UAE. This may be due to the underlying demographic structure of the population in UAE, where the median age of the population is 32.6 years and over 70% are males. The vascular comorbid conditions were also found to be lower in the UAE patients likely because of the same reasons. Other important differences were in the stroke etiologies, where a large majority of the patients from UAE were in the undetermined category. This may again be due to the older patient population from Pakistan, where an underlying atherosclerosis and cardiac source were frequent findings.

The outcomes from patients from UAE were also better compared to those from Pakistan. However, mortality was not significantly different. This again may have to do with the older population from Pakistan with vascular comorbid conditions.

After adjusting for age, stroke subtype and vascular comorbid conditions, COVID-19 was a much stronger predictor of poor outcome in the Pakistani population. This may be due to different severity of COVID infection in the two countries and differences in management protocols for COVID and for strokes related to COVID. More information about the COVID strain, and management protocols might have helped to understand this difference in outcomes between the two countries.

Our study has several limitations. Firstly, we did not collect information on ethnicities of patients from Dubai, UAE. UAE has a multi-ethnic population and although they are predominantly South Asians, it would have been interesting to see if there were other ethnicities with different outcomes. Secondly, we did not collect information on inflammatory markers, which would have added an interesting dimension to the findings. Thirdly, we did not do a centralized classification for stroke etiology, and it was left to the treating neurologist at the respective centers to assign this, which might have added a bias in interpretation. Fourthly, we measured mortality at discharge but did not differentiate whether the mortality was related to COVID or to the stroke itself. Yet another limitation was our inability to follow patients for a 90 day functional outcome. Length of hospital stay is also not a reliable measure since many patients remained admitted due to the pneumonia and often due to quarantine requirements at least in UAE.

Despite these limitations, this is the largest series of COVID related strokes from Asia and confirms that these strokes are of large artery etiology, vascular risk factors are common in these patients and COVID-19 is an independent predictor of poor functional outcomes in these patients. Since the pandemic is not yet over and newer strains are being identified, future studies should focus on how various strains affect the risk and outcomes of strokes and what anti thrombotic treatment is best in these patients.

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Author contributions
Maria Khan: Study Design, Analysis, Manuscript writing and review. Sajid Hameed: Data collection, entry, Analysis, Manuscript review. Bashir Soomro: Data collection, entry, Manuscript review. Samaa Iltaf: Data collection, entry, Manuscript review. Abdul Malik: Data collection, entry, Manuscript review. Saba Farooq: Data collection, entry, manuscript review. Suhail Al Ruqni: Manuscript writing and review. Mohammad Wasay: Study Design, Manuscript writing and review.

Declaration of Competing Interest
None of the authors have any conflicts of interest or disclosures.

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