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In Hospital Mortality and Short-Term Outcomes of Acute Ischemic Stroke Patients Contracting SARS CoV-2 Infection: Experience from a Dedicated Stroke Unit in Bangladesh

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Abstract

Background: The influence of COVID-19 on in hospital mortality and short-term outcome of acute ischemic stroke is not well known. **Objective:** The purpose of the present study was to analyze the overall impact of COVID-19 patients and 30-day outcomes of acute ischemic stroke patients. **Methodology:** This was a hospital-based case-control study from February to May 2021 conducted in stroke unit of National Institute of Neurosciences and Hospital. Consecutive ischemic stroke patients contracting COVID-19 infection was considered as case group and similar patients, negative for SARS CoV-2 on RT-PCR from nasal swab were considered for control group following the inclusion and exclusion criteria. **Results:** A total number of 50 cases and 99 similar control were taken. Although a significant proportion of control group were male (76.8% vs 50%), there was similar age distribution in both groups. Diabetes and Multiple comorbid conditions and lymphopenia were significantly (p value of <0.001) more common among the case (1% versus 22%, 28.3% versus 56% and 5.1% versus 54%) in contrast to hypertension and lymphocytosis which was more frequent in control group (42.4% versus 10% and 94.9% versus 46%). Though the cases had a significantly (p value <0.001) higher NIHSS score at admission (median IQR 7 versus 13) and longer hospital stay (median IQR 6 days versus 14 days). Male stroke patients were 4.7 times more likely to die in-hospital compared to female patients. The risk of mortality were 5 times higher among cases. **Conclusion:** COVID positive stroke cases have more severe disease at admission and longer hospital stays and the risk of mortality is 5 times higher in COVID positive stroke cases with a significant male dominance. *[Journal of National Institute of Neurosciences Bangladesh, January 2023;9(1):11-15]*

Keywords: COVID 19, Ischemic Stroke, Hospital Outcome

Introduction

After initially being reported as acute respiratory illness in Wuhan. China, COVID-19 was also found to involve cardiovascular and neurologic system[1-3]. SARS CoV-2 has high affinity to ACE-2 receptor which is abundant in vascular tree in addition to the respiratory epithelium. Though neurologic dysfunction is observed in around 36.4% of COVID-19 patients, ischemic stroke had been reported among 0.9% to 2.7% of the COVID-19 patients[4-6]. If you take the proposed pathophysiologic mechanism in consideration, ischemic events are likely to happen in COVID-19 patients[7-9]. Although a significant increase in large vessel occlusion (LVO) had been reported from Dubai and New York at the initial phase of the pandemic, later on the completely different scenario of stroke admission was also reported from Europe and Asia[9-13].

SARS CoV-2 impose a higher risk of stroke than other influenza virus[14]. Several studies have reported a difference in clinical profile and biochemical parameters of COVID-19 related stroke cases. These patients are significantly younger male with severe clinical presentation, more comorbidity, lower platelet and leukocyte counts, and higher levels of D-dimers, cardiac troponin I and interleukin-6[9-11].

Considering the difference in clinical and biochemical

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profile of COVID positive stroke cases, in hospital mortality and further outcome is also expected to be different from the COVID negative stroke patients. Taking the pathophysiologic mechanism in consideration, further in-depth analysis is warranted. Henceforth, it had been decided to conduct this case control study to examine the difference in hospital mortality and short-term outcome of ischemic stroke patients contracting SARS CoV-2.

Methodology

Study Settings and Population: This was a hospital-based case control study conducted between February to May, 2021. Data from both the cases and control were collected from 100 bed stroke unit of National Institute of Neuroscience & Hospital (NINS&H). Fifty consecutive COVID positive ischemic stroke patients were included as cases and 100 COVID negative ischemic stroke patients as control. Both the male and female patients aged 18 years and above were included. RT-PCR from nasal swab for SARS CoV-2 based study from nasal swab within 96 hours of stroke onset. The cut-off point was decided on the basis of pathophysiology of viral load which is usually at its peak within 96 hours of infection and it is very highly unlikely to be tested positive within this time if the infection is acquired after hospital admission.

Study Procedure: The operational definition for ischemic stroke (IST) were taken from AHA/ASA Expert Consensus Document on Updated Definition of Stroke for the 21st century15. The COVID-19 cases were defined according to the National Guidelines on Clinical Management of Coronavirus Disease 2019 (Covid-19) 16. Data were collected by a semi-structured questionnaire by the recruited research officer. The collected data was verified later on by the investigators. As NINS&H was not a COVID designated hospital and once any patients of stroke detected with SARS CoV-2 was referred to Government designated COVID hospitals; the selected cases and control were then interviewed by the research officer over telephone for further assessment of the outcome. Outcomes at discharge from hospital and at the end of 30 days were measured through modified Rankin Scale score. The median NIHSS score at admission and mRS score at discharge and at the end of 30 days were compared among both the study groups. The primary end point was death or mRS at discharge from hospital and the secondary end point was the mRS at 30 days.

Statistical Analysis: The demographic and clinical characteristics between COVID positive IST cases and COVID negative controls were compared. Pearson Chi-square test, Mann-Whitney U test and Fisher's Exact test were used wherever applicable. However, Bonferroni correction is applied to adjust level of significance when multiple tests are performed in categorical variables with multiple categories. Step-wise backward logistic regression was also done to identify any significant association between in-hospital outcome and demographic and clinical risk factors. Data analysis was done by Statistical Package for Social Sciences (SPSS) version 21 and R version 4.0.0.

Ethical Clearance: All the procedures of the present study were carried out in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles for human investigations (i.e., Helsinki Declaration) and also with the ethical guidelines of the Institutional research ethics. Before starting the study, the study protocol, patient information sheet, and informed consent form were approved by the independent ethics committees of the study place and the competent regulatory authorities in accordance with local legal requirements in participating center. Formal ethics approval was granted by the Institutional Review Board of National Institute of Neurosciences and Hospital. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and analyzed using the coding system.

Results

In this study we lost one patient from control group during follow up. So, we had a total of 99 COVID negative control (group A) and 50 COVID positive ischemic stroke cases (group B). Though there was no significant difference in age group among case and control but there was significantly higher proportion of male in control group (76.8% and 50%) with a p value

Table 1: Distribution of all patients by age and Gender (n=166)

Characteristics	Case (n=50)	Control (n=99)	P Value
Age Group			
≤50 Years	11 (22%)	15(15.2%)	0.479
51 to 60 Years	13 (26%)	33(33.3%)	
>60 Years	26 (52%)	51(51.5%)	
Gender			
Female	25 (50%)	23 (23.2)	0.002
Male	25 (50%)	76 (76.8)	

of 0.002. Most of the patients in Group A and B were aged 60 years and above (51.5% and 52%, respectively) (Table-1).

The comparison of clinical profile and hospital course of the patients is presented in Table 2. There was no statistical difference in clinical presentation among the groups except for loss of consciousness (LOC) which was more frequent (39.4%) in control group (p value <0.001). Diabetes and Multiple comorbid conditions were more common in Group B (1% versus 22% and 28.3% versus 56%) whereas Hypertension was more common in Group A (42.4% versus 10%), The differences were statistically significant with a p value of <0.001 (Table 2). While lymphocytosis was significantly (p value <0.001) more common in group A (94.9% versus 46%), lymphopenia was observed in group B (5.1% versus 54%). There was no significant difference in requirement of ICU among the groups as well as in hospital outcome in terms of mortality and improvement (Table 2). Though the patients in group B had a significantly (p value <0.001) higher NIHSS score at admission (median IQR 7 versus 13), longer hospital stay (median IQR 6 days versus 14 days) which was also statistically significant (p value <0.001) (Table 2). But there was no significant difference among the groups in mRS at discharge (median IQR 3) and at 30 days with a median IQR of 2 (Table 2).

Table 2: Distribution of all patients by clinical characteristics and outcome (n=149)

Characteristics	**Case (n=50)**	**Control (n=99)**	**P Value**
Clinical Presentation	**Number (%)**	**Number (%)**	
Aphasia	4 (8%)	2 (2%)	ns
Cortical Blindness	2 (4%)	0	ns
Dysphasia	4 (8%)	3 (3%)	ns
Hemiplegia	3060	50 (50.55%)	ns
LOC	5 (10%)	39 (39.4%)	<0.001
Multiple	5 (10%)	55 (55.1%)	ns
Comorbidity			
DM	11 (22%)	1 (1%)	<0.001
HTN	5 (10%)	42 (42.4%)	<0.001
IHD	0	6 (6.1%)	ns
Multiple	28 (56%)	28 (28.3%)	0.001
None	6 (12%)	22 (22.2%)	ns
WBC			
4-11	17 (34%)	24 (24.2%)	ns
>11	33 (66%)	75 (75.8%)	
ALC			
<=1	27 (54%)	5 (5.1%)	<0.001
>1	23 (46%)	94 (94.9%)	
ICU Support			
Yes	7 (14%)	6 (6.1%)	ns
No	43 (86%)	93 (93.9%)	
Outcome			
Dead	10 (20%)	22 (22.2%)	ns
Improved	40 (80%)	77 (77.8%)	
	Number (n)/ Median IQR	**Number (n)/ Median IQR**	**P Value**
Hospital Stay	50/ 14 (10-20)	99/ 6 (3-7)	<0.001
NIHSS Score	50/ 13 (7-17)	99/ 7 (3-13.2)	<0.001
mRS at Discharge	50/ 3 (2-4)	99/ 3 (2-5)	ns
mRS at 30 days	40/ 2(1-2.25)	77/ 2(1-3)	ns

*LOC= Loss of consciousness, WBC- White Blood cell, ALC- Absolute Lymphocyte Count

We use binary logistic regression model to investigate association between patient in-hospital morbidity and demographic and clinical risk factors. Due to limited sample sizes, we applied backward stepwise method for selection of the significantly important variables and consequent parsimonious models. The result is presented in table 3. Male stroke patients are 4.7 times more likely to die in-hospital compared to female patients. Covid infection and higher NIHSS scores of stroke patients have significant positive association with the likelihood of death after controlling for other potential risk factors. Covid positive stroke cases are 5 times more likely to die compared to patients who were not infected. For NIHSS scores, a one unit increase in the score is associated with almost 17% increase in the odds of dying. The other significant risk factor is LOC (Table 3).

Table 3: Results binary logistic regression to investigate association between patient morbidity and demographic and clinical risk factors

Term	**Estimate**	**P value**	**Confidence low**	**Confidence high**
(Intercept)	0.003	0.000	0.000	0.018
Sex-Male	4.711	0.010	1.539	16.785
Covid-Positive	5.027	0.013	1.471	19.361
LOC	7.690	0.001	2.509	26.628
NIHSS Score	1.167	0.000	1.077	1.278

Discussion

This study shows the impact of SARS CoV-2 positivity on outcome of acute stroke patients in terms of in hospital mortality and mRS at 30 days. Ninety nine COVID negative controls with 50 COVID positive stroke patients were analyzed. Study revealed that COVID positive stroke cases were more likely to be diabetic and had multiple co-morbidities. They had

higher NIHSS score at admission, longer length of hospital stays, more chance of developing lymphopenia and higher risk of mortality.

In a systemic review and meta summery of literature Tan YK et al reported the clinical and biochemical profile of COVID positive ischemic stroke cases[17]. Similar to the report majority of the study patients were 60 years or older. The systemic review also reported that Hypertension, diabetes and dyslipidemia are the common co-morbid conditions in COVID positive stroke. In this study, diabetes and multiple co-morbidities were significant association in COVID positive ischemic stroke. Similar to the original reports from Wuhan, China in 2019, there were significant association of COVID related lymphopenia in ischemic stroke patients[18]. These finding also supports the observation from multicenter study in New York and UK that the COVID positive ischemic stroke cases have higher NIHSS score on admission and longer duration of hospital stays[19,20]. Both the NIHSS score and length of hospital stay were even much higher in this study. Though the study from New Yok compared the COVID positive IST cases with historical control, this study assed the cases with controls from the same settings at the same time. This excluded the bias towards the impact of COVID-19 on the admission behavior of patients at hospitals. It is established that minor stroke cases usually avoided hospital admission during the pandemic[12,21]. It is obvious that the group with more severe disease at admission are more likely to have longer length of hospital stay.

Perry et al. reported that COVID-19 infection is independently associated with higher mortality even after correction of the parameters known for the early mortality[20]. After correction of confounders this study confirms the notion that COVID-19 infection is independently associated with 5 times higher risk of in hospital death. Havenon et al. also observed a four-fold increase in mortality comparing the data from 46 centers in USA[22]. But this observation contradicts the finding of SETICOS Collaborators on mRS score at discharge[20]. Though they reported a significantly higher median mRS at discharge among case (4 versus 3), this study did not find any change in median mRS at discharge or at 30 days[20]. This is probably due to smaller sample size and shorter length of follow up time.

Despite several limitations, the major strength in these data series is the use of contemporaneous control from the same hospital even during this pandemic, while several studies constructed historical control group. But the major limitation was relatively smaller sample size and inability to match the controls with each case individually. But the effect was minimized by using backward regression model for the variables of interest.

Conclusion

COVID positive ischemic stroke patients are more likely to be diabetic or have multiple co-morbidities and have Lymphopenia. These patients have longer length of hospital stay. But there is no difference in morbidity at discharge or at short term follow up. The risk of in hospital mortality higher among COVID positive ischemic stroke patients. Irrespective of the COVID status, male stroke patients have higher chance of dying and every unit increase in the NIHSS s score is associated with increase in the odds of death.

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