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Original Article

Acute Ischemic Stroke in Relation of COVID-19

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Abstract

Introduction: *In 21st century, the miserable medical condition is still Corona virus disease 2019 (COVID-19). It is such a pandemic disease that was unexpected by this generation. The culprit organism by which the whole world embraced is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Involvement of respiratory system with such notorious microorganism enhances hypoxaemia. Hypoxia and other procoagulant including platelet increment in COVID-19 accelerate ischemic stroke. Our aim is to observe the effects of COVID-19 on pro-coagulation and platelet dysfunction that enhance ischemic stroke.*

Materials and Methods: *Total 108 patients were diagnosed as SARS-CoV-2 and had been first time reported & were admitted in Combined Military Hospital (CMH) Mymensingh, within 1st March 2020 to 18th May 2021. Total 108 patients were randomly selected and divided into two groups one with simple form and another with severe disease, procoagulation-morbidities, coagulation disorder- specially D-dimer positive COVID-19 disease. Out of those 108 patients simple variety of COVID-19 were 56 (51.85%) and Complex COVID-19, 52(48.15%) patients.*

Diagnosis was done based upon details patients' history, clinical examination, haematological test, radiography of chest and confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR).

Results: *Out of the 108 COVID-19 patients, males were 88(81.48%); females were 20(18.52%) and males were predominant.COVID-19 Incidence among the age group; 10-19 years 07(6.48%), 20-29 years 38(35.19%) and 30-39 years 34(31.48%), 40-49 years 20(18.52%), 50 years or more 9(8.33%) in number and mostly affected in young adult &adult. Regarding Procoagulant; D-dimer positive 13(59.09%), Thrombocytosis 6(27.27%) and Mixed 3(13.64%) patients and mostly D-dimer positive. Out of 108 patients; Simple 56 (51.85%) and Complex COVID-19, 52(48.15%) patients. Of complex COVID-19 that prone to ischemic stroke; Procoagulant 22(42.31%), CVS disorder 10(19.23%), DM 5(9.62%), Severe Pulmonary lesion 8(15.38%), Multiple-comorbidities 7(13.46%) patients and Procoagulant is predominant. Only 3(2.78%) were diagnosed as Acute Ischemic stroke and treated promptly.*

Amongst 108 patients, 4(four) patients were died ; 1st one with heart failure , 2nd one with HTN,MI , 3rd one with HTN, Old haemorrhagic stroke and last one with CKD,ARDS and most of them are above 50 years of age. And fortunately no patient had died with ischemic stroke as preventive measure with anticoagulant with or without thrombin inhibitor utilized for complex COVID-19.

Conclusion: *Coagulum is the crucial factor of ischemic stroke.COVID-19 can produce severe pulmonary lesion followed by hypoxia to polycythemia, prothrombotic state and thrombocyte dysfunction. This procoagulation enhance acute ischemic stroke.*

Abbreviations: *COVID-19-Corona Viral Disease-19,SARS-CoV-2-Severe Acute Respiratory Syndrome Coronavirus-2,RT-PCR-Reverse Transcription Polymerase Chain reaction ,CMH-Combined Military Hospital, CT Scan -Computed Tomography Scan.*

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Introduction:

The World Health Organization (WHO) declared COVID-19 as pandemic disease in March 11th, 2020[1]. The whole world did not see such a global pandemicity in last century. What a scarcity of scientist and medicos at this age till date. We heard before, but couldn't imagine we will have to face this one. No one knows how many wave we will carry and its time limit of happy complete ending. SARS-CoV-2 is continuous changing its genetic material (mutation) at least thousands time till today. We thought once vaccine inoculated it will be ruined; but unfortunately in some instances single dose even double doses vaccination could not kill properly the notorious organism. Now in the world; COVID-19 is the single most medical issue. SARS-CoV-2 organism spreading too fast worldwide after 1st diagnosed in December 2019, Wuhan, China[1].

Risk factors of stroke are commonly hypertension (HTN), smoking, alcohol, lipid disorder, DM, arrhythmia and previous stroke[2].COVID-19 mostly affects respiratory system which leads hypoxaemia to coagulopathy; and is the main factor of ischemic stroke[3,4].Acute ischaemic stroke are more with severe COVID-19 than with non-severe disease[5].The patient's mortality rate is higher in COVID-19 with history of cerebral stroke compared without any history of stroke of COVID-19 patients[6].

The mechanism of COVID-19 related to ischaemic stroke is still poorly understood. Pulmonary lesion leads to hypoxaemia related early growth response-1 (Egr-1) activation that exaggerates transcription/translation of tissue factor followed by acceleration of intravascular deposition of fibrin. It also suppresses fibrinolytic activity by up regulation of plasminogen activator inhibitor-1 and concomitant enhance procoagulation[7].

SARS-CoV -2 also accelerates prothrombotic state and obviously induces arterial and venous thromboembolic manifestation and thrombocytosis enhanced thrombosis; lead to ischemic stroke[8].

Covid-19 is one of the potential risk of cerebrovascular disease that increase morbidity even mortality[9,10].

Once procoagulation is evident; early therapeutic anticoagulation and/or anti-platelet should start to reduce thromboembolic manifestation of patients with COVID-19-associated ischaemic stroke. But keeping mind, there is risk of intracranial haemorrhage; including haemorrhagic transformation of cerebral infarct.

Pathogenesis:

Ischemic and haemorrhagic stroke are two types of cerebral stroke and mostly ischemic stroke; even in COVID-19 related stroke; 10% is haemorrhagic and 90% ischemic one[6].

Narrowing of the lumen of blood vessel by thrombotic mass or clogging by embolus arising from the heart or remote parts of the body are usual phenomena of ischemic stroke.

Coronary diseases are the obvious source of emboli specially in cardiac arrhythmia. HTN, hyperlipidemia and atherosclerotic changes produce narrowing of blood vessels followed by reduction of blood supply to brain- induced; ischemic stroke[2].

DM is abnormal glucose metabolism that leads to chronic hyperglycemia and also effects on protein and lipid metabolism. This phenomenon produces microangiopathy-changes in specially small vessels like renal, neural and retinal blood vessels and enhanced atherosclerosis. And it also induce macroangiopathy-in large and medium sized blood vessels e.g. the heart, limbs and brain[11].

The exact mechanism of ischemic stroke in COVID-19 still under investigation. SARS-CoV-2 binds with the ACE2 receptor and gets entry into human cell. ACE2 receptor is expressed in type 2 alveolar epithelial in the kidney, heart and gastrointestinal tract and abundant in lung. So in COVID-19, local inflammatory response is direct injury to the lung tissue; is one of the mechanisms of respiratory manifestations[12].

In severe condition, alveolar sac is filled with mucus, fluid and anti-inflammatory cells lead to pulmonary consolidation and consequently difficulty of pulmonary gas-exchange specially oxygen[13].

Cytokine storm syndrome (CSS) is the enhanced immune response; triggered by SARS-CoV-2 infection due to excess proinflamatory and inadequate anti-inflammatory response[14].

In COVID-19, CSS involves multiorgan and induce acute respiratory distress syndrome (ARDS), renal and cardiac injury[15].

CSS and hypoxia usually occur simultaneously lead to acceleration of coagulopathy and platelet activation. Hypoxia helps to platelet–monocyte formation, enhance platelet activity and direct activation of coagulation[16].

Severe inflammation of respiratory system by SARS-CoV-2; followed by pneumonia, substantial pulmonary oedema, pulmonary consolidation and respiratory failure result inadequate gas exchange, hypoxia induced polycythemia and coagulopathy[2].

In COVID-19; hypoxaemia that influence polycythemia, platelet disorder and coagulopathy are the vital factors of ischemic stroke[3,4].

Another hypothesis COVID-19 associated ischemic stroke- notorious SARS-CoV-2 virus is associated with severe inflammatory response syndrome (SIRS) accompanied by coagulopathy with elevated D-dimer level and presence of antiphospholipid antibodies, have high prevalence of thrombosis[3,17,18].

SARS-CoV-2 infection is also related to prothrombotic state, which induces arterial and venous thromboembolism & elevated D-dimer level. In severe COVID-19, pro-inflammatory cytokines activate endothelial & mononuclear cell with expression of tissue factor lead to activation of coagulation and thrombin generation. Circulating free thrombin is uncontrolled by natural anticoagulants, may activate platelet enhanced thrombosis[8].

COVID-19 also accelerates thromboembolism and thrombocytosis with thrombosis; that enhance ischemic stroke[8].

COVID-19 patients are high risk for enhancing medical complications, such as myocardial infarction, heart failure, and arrhythmia, myocarditis, arterial &venous thrombosis. All of them largely contribute in ischemic stroke[19].

Baseline risk factors for cerebral stroke specially ischemic one, such as HTN and coronary artery disease, arrhythmia, DM are more common in patients with COVID-19. Unidentified other factors related to COVID-19 may play a role in increment of stroke beyond observation of other viral infections is now require for further investigation.

Investigation:

In COVID-19; laboratory findings are elevated serum proinflammatory cytokines, cytopenias- mainly leukopenia, thrombocytosis, increased ferritin and D-dimer level[15].

And also interleukin-6, D-dimer, troponin and N-terminal pro-brain natriuretic peptide level remarkably elevated in contemporary COVID-19 cases with stroke symptoms[6].

COVID-19 patients and ischemic stroke study, done by Yaghi et al [20]., had not only higher D-dimer level in COVID-19 cases but also elevated troponin and erythrocyte sedimentation rate ;when compared with ischemic stroke patient of COVID-19 and patients non infected by SARS-CoV-2 virus.

The common abnormalities in SARS-Cov-2 infection are elevated D-dimer and fibrinogen[21].

Regarding radiological findings- Plain Chest X-ray may be normal in early/mild COVID-19 and hospitalized cases 69% had an abnormal chest radiograph during the time of admission and 80% had radiographic abnormalities within few days of hospitalization. Most extensive lesion is evident about 10-12 days after symptom onset. Common radiological findings are airspace opacities, whether described as consolidation or less commonly ground glass opacity (GGO) and ill-defined opacification. The most distribution is often peripheral, bilateral and lower zone but may be unilateral and the pleural effusion is rare (3%)[22].

D-dimer: Fibrin degradation product is D-dimer; formed in degradation of blood clot by fibrinolysis. Its normal value is Â250 ng/ml[23].

D-dimer positive means Ã250 ng/ml revealed thrombotic disorder. Increased D-dimer level is associated with high risk of stroke mainly ischemic one and as it is easily accessible and inexpensive marker; had great value for prevention of ischemic stroke[24].

SARS-CoV-2 is linked with prothrombotic state, elevated D-dimer level; are thromboembolic inducer[8].

All patients who were COVID-19 with ischemic stroke had D-dimer positive and those who were severe in nature, had elevated LDH and ferritin[25].

The systematic investigation should be done for understanding the mechanism, characteristics and short-term outcome of acute cerebral ischemic stroke of patients with SARS-CoV-2 infection. Most ischemic stroke occurred in old age and those with have traditional risk factors of stroke. Plasma D-dimer level were 3-fold higher in those who with have ischemic stroke than who did not[19].

Regarding CVS and metabolic disorder; Lipid profile, blood sugar, HbA1c, ECG and Echo-cardiogram may require to identify risk of ischemic stroke.

If COVID-19 had features of inclination to ischemic stroke or definitive one; anti-coagulant, anti-platelet and even intervention, such as thrombolysis and thrombectomy, can be instituted. Framingham and Rochester in their stroke study showed, the mortality rate at 30 days after ischemic stroke was 19%, and the 1-year survival rate of patients with ischemic stroke was 77%. Prognosis of acute ischemic stroke also varies greatly in individual patients, depending on the stroke severity, co-morbidity, age and post-stroke complications[26].

But at least 23% casualties occur in ischemic stroke patients at first year; and if associated with COVID-19 definitely death rate will be excessive.

In this background to come into conclusion we tried to identify prothombotic state prone to ischemic stroke in COVID-19 patients. So that we can take promptly preventive measure in secondary care hospital like CMH Mymensingh, Bangladesh.

Materials and methods:

This study is a prospective study. All patients with COVID-19 who were admitted and confirmed diagnosis just after admission in CMH, Mymensingh, during the period 1st March 2020 to 18th May 2021 were enrolled for the study.

Total 108 patients in either sex & age variables were randomly selected. Patients of this study were divided into two groups one with simple COVID-19 and another complex COVID-19 with procoagulation disorder and co-morbidities like D-dimer, thrombocytosis and severe form of disease. Out of 108 patients simple COVID-19 were 56(51.85%) and complex 52(48.15%).

The whole world is now in catastrophe with corona disease and Bangladesh is not out of them. All of our patients were analyzed and evaluated in Mymensingh CMH. Clinical, haematological, biochemical, RT-PCR, radiological data of patient was recorded from hospital record, picture archive and communication system. Patients with COVID-19 having co-morbidity or not were included. All cases were most reliable test RT-PCR sorted and included in this study. Patients of age group 10 years and above with irrespective of gender, co-morbidities such as HTN, hypercholesteromia, DM, MI; on anticoagulant, coagulopathy etc. were included in our study. Evaluation of patients by details history, clinical examination and relevant investigation was done until corona virus negative but patient without COVID-19 and consent not given were excluded.

Results:

A total 108 COVID-19 patients were evaluated by details history, clinical examination & relevant investigation.

Table-I

Distribution of patients according to sex (n=108)

Male	Female	Total
88(81.48%)	20(18.52%)	108(100%)

Amongst 108 COVID-19 patients, maximum patients 88(81.48%), were male (Table-I).

Table-II

Distribution of patients according to age (n=108)

Age(years)	Frequency	Percentage (%)
10-19	7	6.48
20-29	38	35.19
30-39	34	31.48
40-49	20	18.52
≥50	9	8.33

Out of 108 patients, maximum patients 38(35.19%), were in age range 20-29 years, young adult (Table-II).

Regarding Procoagulant; out of 22 patients, D-dimer positive 13(59.09%), Thrombocytosis 6(27.27%) and Mixed 3(13.64%) patients and mostly were D-dimer positive(Figure-1).

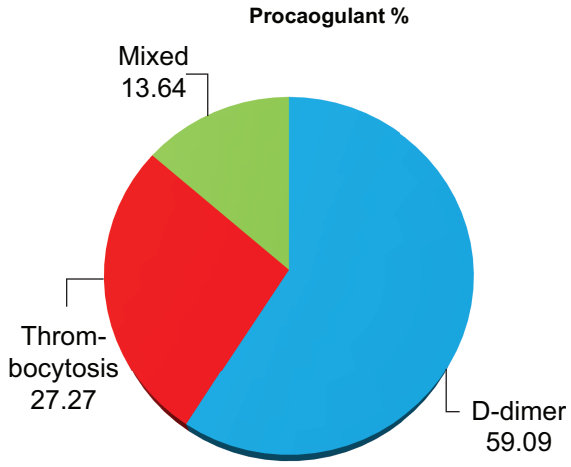

Fig-1: *Distribution of Procoagulant*

Regarding COVID-19; Simple 56 (51.85%) and Complex 52(48.15%) patients. Amongst complex COVID-19; Procoagulant 22(42.31%), CVS disorder 10(19.23%), DM 5(9.62%), Severe Pulmonary lesion 8(15.38%), Multiple-comorbidities 7(13.46%) patients and Procoagulant is predominant 22 (42.31%) (Figure-2).

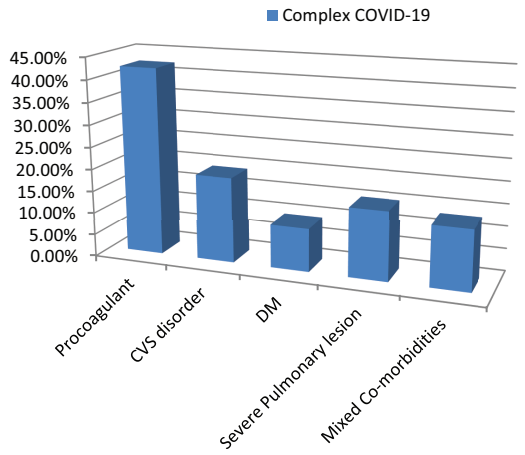

Fig-2: *Distribution of complex COVID-19*

Table-III
Distribution of patients with Stroke (n=108)

Ischemic Stroke	Haemorrhagic Stroke	Total
3(2.78%)	Nil	108(100%)

Out of 108 patients no one found haemorrhagic Stroke, rather 3(2.78%) patients only suffered from Ischemic Stroke as prophylactic measure taken on time after observing marker inclination to Stroke(Table-III).

Discussion:

SARS-CoV-2 infection more prone to pulmonary injury. In severe cases pulmonary consolidation develop and difficult for oxygen-exchange[13].Hypoxaemia influence polycythemia, platelet disorder and coagulopathy are the vital factors of ischemic stroke[3,4].SARS-CoV -2 also accelerates prothrombotic state and obviously induce venous & arterial thromboembolism and thrombocytosis that enhance thrombosis; leads to ischemic stroke[8].New York stroke center illustrated that there is high risk of severe stroke syndromes in young patients affected by COVID-19[27].Shadi Yaghi et al[20]., stated that COVID-19 positive patients mostly were younger man.

Alexander E et al[19]., showed that COVID-19 affected population; the median age was 64 years (51-76 years), 43% were female and 57% were men.

There is a study in Palestine conducted by WHO; revealed that most COVID-19 population were women 54.78% and man 45.22% and mostly affected age group 18-29 years 35.65%[28].

In our study, males were 88(81.48%); females were 20(18.52%) in number & males were predominant which is similar to the study of Shadi Yaghi et al., as soldiers of Bangladesh army are mostly male personnel[20].

Incidence of COVID-19 of this study; among the age group; 10-19 years 07(6.48%), 20-29 years 38(35.19%) and 30-39 years 34(31.48%), 40-49 years 20(18.52%), 50 years or more 9(8.33%) in number and mostly affected in young adult which is similar to the study in Palestine; done by WHO, as our serving soldiers are mostly young adult[28].

SARS-CoV -2 infection induced local inflammatory response is the direct injury to the pulmonary tissue; and its consequences may produce pneumonia, pulmonary oedema, consolidation and or ARDS.According to Bernheim et al[29]., radiological findings of respiratory system in COVID-19; no findings 22%, 34% ground glass, consolidation 2%, rest mixed and bilateral 60%.

COVID-19 usually having elevated serum proinflammatory cytokines, cytopenias- mainly leukopaenia, thrombocytosis, increased ferritin and D-dimer level lead to ischemic stroke described by Mehta P et al[15].

Most common abnormalities in COVID-19 are elevated D-dimer, fibrinogen[21].

Regarding Procoagulation of this study; D-dimer positive 13(59.09%), Thrombocytosis 6(27.27%) and Mixed 3(13.64%) patients and mostly D-dimer positive, which is similar to Mehta P et al., study[15].

There is more chance of ischemic stroke as well as casualty in patients with D-dimer positive, increased procoagulation factors and other risk factors HTN, DM, dyslipidemia with MI, arrhythmia, hypoxia(pulmonary oedema) that are enhanced by COVID-19. There is a study suggestive of increase stroke with a 2.5- fold in severe COVID-19 and increase mortality rate[30].

In our study; factors enhancing ischemic stroke in COVID-19 (Complex variety- 52 patients) Procoagulant 22(42.31%),CVS disorder(HTN, dyslipidemia with MI, arrhythmia) 10(19.23%), DM 5(9.62%),Severe Pulmonary lesion 8(15.38%), Multiple-comorbidities 7(13.46%) patients as similar to the study done by Aggarwal G et al[30].

In our study no one found haemorrhagic Stroke, rather 3(2.78%) only suffered from Ischemic Stroke as prophylactic measure taken on time after observing marker inclination to Stroke.

Therapeutic anticoagulation in high D-dimer and enhanced procoagulation evident patients may reduce thrombotic complications specially ischemic stroke of COVID-19 positive patients[20].

In our study in CMH Mymensingh; although four patients died but fortunately no one died by ischemic stroke as we used anticoagulant with or without thrombin inhibitor for complex COVID-19.

In this study, there are some limitations - it was done in a single center, CMH Mymensingh, less number of patients and short duration of study. But as whole country is affected by COVID-19 and our patients are entitled both serving, retired soldiers & parents of our military members live different parts of the country and reported to our CMH Mymensingh which reflects overall scenario of Bangladesh.

Conclusion:

SARS-CoV-2 infection may produce severe pulmonary lesion leads to coagulopathy; coronary disease, DM also influence prothrombotic state- are crucial factors for ischemic stroke. SARS-Cov-2 elevate procoagulant specially D-dimer that express high prevalence of thrombosis leads to ischemic stroke. So in COVID-19, prothrombotic state should be scrutinized and address properly to reduce ischemic stroke insult as well as diminution of morbidity and mortality.

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