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Original Research Paper

Association of Covid 19 Infection with Spontaneous Subarachnoid Hemorrhage in ICU Patients

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ABSTRACT:

Background: Covid-19 infection may necessitate ICU admission and mechanical ventilation support due to acute respiratory failure. Apart from respiratory decompensation, neurological manifestations are found to be quite common. **Objective**: The aim of this study is to evaluate the association of spontaneous subarachnoid hemorrhage and factors related to it. **Study Design**: This retrospective observational study was conducted from February 2020 to August 2022 at Intensive care unit, The Children's Hospital and Institute of Child Health, Faisalabad. **Results**: During pandemic, out of 563 covid 19 ICU patients on mechanical ventilator, 48 patients developed subarachnoid hemorrhage at our setup. (n=48, 8.5%, 95% CI [2.43-4.95], RR=0.76) The levels of inflammatory markers were in congruence with the severity of the disease ($P < 0.037$). Out of 48 patients, 29 patients had comorbidities, 21 patients fully recovered without any deficit and 5 patients died. **Conclusion**: Subarachnoid hemorrhage is one of the common manifestations of covid 19 infection. CSF analysis is found more sensitive than CT brain plain to detect (grade 1) subarachnoid hemorrhage. The severity of covid infection and development of associated subarachnoid hemorrhage was significantly related to the presence of pre-existing comorbidities, and the extent of hematological and CSF profile derangement. However, the relation between the duration of hospital stays, severity/duration of covid 19 and subarachnoid hemorrhage is found insignificant.

Keywords: Neurocovid, covid-19, subarachnoid hemorrhage, pediatrics, pathophysiology, mechanical ventilation

INTODUCTION:

Coronavirus 2 (Covid-19, named by WHO on Feb 11, 2020) strain has caused Coronavirus disease in 669 million people, globally with 6.74 million deaths so far. [1] As of 12 Jan 2023, 15,265,472 pediatric cases of covid 19 have been recorded, accounting for 18.1% of total cases at the rate of 20,282 cases per 100,000 children in the population worldwide. [2] All time cases of covid 19 in Pakistan are 1.58M with 30,640 deaths to date. [3] The exact pediatric population affected by covid infection is unknown. Several associations have been established with the covid 19. One of them is subarachnoid hemorrhage, a life-threatening condition, resulting in 5-10% strokes in USA (5-10 cases per 100, 000 annually). [4] According to multiple studies, the incidence of COVID-SAH ranges from 0.3%-1.4%. [5, 6] Total cases of COVID 19 are still climbing on daily basis despite the worldwide provision of vaccines and all the necessary preventive measures. In Pakistan and all the other developing countries, the actual number of COVID cases were far higher than the documented cases, mainly due to lack of funds and additional burden on the health system. [7] With plenty of literature proving the association of covid 19 with spontaneous subarachnoid hemorrhage, Neuro Covid is a new

medical entity now. [7, 8] The coronavirus infection is known to have several effects on brain and mental health including neurological, neurophysiological, and neuropsychiatric changes with acute and insidious, long term neurodegenerative disorders. [8, 9] Several studies with significant results have shown the spectrum of central nervous system (CNS) and peripheral nervous system (PNS) involvement associated with the acute and chronic course of covid 19 infection. [9, 10] Acute neurocovid-19 symptoms include altered state of consciousness, encephalitis, encephalopathy, dizziness, headache, hypogeusia, hyposmia, encephalitis, ischemic stroke, cerebrovascular injury, and neuropsychiatric manifestations. Subarachnoid hemorrhage is found to be more common in children with pre-existing neurological disorders, comorbidities, and anticoagulation therapy. [10] The pathophysiological and postmortem studies of covid 19 infection have also described cerebral venous sinus thrombosis and reversal cerebral vasoconstriction syndrome in affected patients. In covid infection and viral overload, thrombosis can be a consequence of hypercytokinemia, hypercoagulability state (coagulopathy or immune thrombocytopenia), and/or endothelial damage. [11] Thrombus formation can cause ischemic stroke which later can cause hemorrhagic stroke as a result of reperfusion injury. The exact pathophysiological pathway of neuroinvasion of coronavirus is unknown. Nonetheless, the presence of aneurysm is found to make the patient more susceptible to developing intracranial hemorrhage. [11, 12]

COVID 19 patients often require mechanical ventilation due to ARDS and respiratory failure. Mechanical ventilation needs continuous monitoring and manual adjustments according to the patient's status. A balance between blood oxygenation and cardiac output maintenance is pivotal. [13] Optimal blood oxygen levels and carbon dioxide are essential for adequate cerebral perfusion. Hypoxemia and hypocapnia are related to cerebrovascular compromise and SAH consequently. Carbon dioxide level ($PaCO_2$) < 35 mmHg is found to be associated with the increased morbidity and sudden deterioration of GCS (<4). Carbon dioxide is a potent vasomodulator and presumably, hypocapnia is strongly associated with vasospasm leading to spontaneous subarachnoid hemorrhage. The risk of SAH increases in the presence of aneurysm. The rise in intracranial pressure (ICP) due to hypocapnia is still the matter of debate. If true, then the increase in ICP due to hypocapnia could be another cause of developing SAH on mechanical ventilation. [13, 14] This study mainly focused on the evaluation of association between the COVID 19 and subarachnoid hemorrhage. The cases were evaluated on their clinical, pathological, radiological, and demographic factors. The purpose of this study was to probe the cause of spontaneous SAH in confirmed cases of COVID 19 patients in order to dodge the causative factors of this complication in future.

Inclusion criteria:

- Confirmed covid 19 cases in pediatric age group with age ranging from 1 year to 14 years.
- Patients who required mechanical ventilation for the treatment of severe respiratory distress due to covid infection
- Patients with normal coagulation profile
- Patients who developed subarachnoid hemorrhage in the course of Covid-19 infection

Exclusion criteria:

- Development of subarachnoid hemorrhage prior to covid infection
- Cases in which guardians of the patients refused a certain treatment/investigation such as lumber puncture, mechanical ventilation, etc.
- Patients on anticoagulation/antiplatelet therapy for covid infection or any other comorbidity i.e., cardiac disorder
- Patients with incomplete data or patients who were discharged on request amidst treatment were also not included in this study.

MATERIAL AND METHODS:

This retrospective study was conducted at a comprehensive intensive pediatric care unit of Children's Hospital Faisalabad, Pakistan. The data was collected from the revision of the chart and previous documents extracted from the record room. According to the data collected, the children with the respiratory infection were clinically evaluated for the signs and symptoms of covid 19 infections. From the suspected cases, clinical specimens via nasopharyngeal swab were collected, as per WHO recommendation. [15] The swabs were placed into preservation solution containing tubes. The diagnosis of SARS Covid-19 was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR). High resolution computed tomography (HRCT) chest was also performed to evaluate the extent of lung involvement. The Cranial CT scan was used to diagnose subarachnoid hemorrhage (SAH). The SAH was further categorized by using Fisher grading scale.

Grades	Description
Fisher Grade 1	No blood detected
Fisher Grade 2	Diffused deposition or thin layer <1mm thick with all vertical layers of blood in interhemispheric fissure, insular cistern, and ambient cistern
Fisher Grade 3	Vertical layers of blood ≥1mm thick or localized clots
Fisher Grade 4	Intracerebral or intraventricular clots with diffused or no subarachnoid hemorrhage

Table 1. Fisher Grading for Subarachnoid Hemorrhage

Non-traumatic lumber puncture was performed for CSF analysis, mainly for occult subarachnoid hemorrhage, glucose and protein content, and WBC count. Blood samples were taken to assess complete blood count, erythrocyte sedimentation rate (ESR), coagulation profile, CRP, LDH, and D-dimer. The modified Rankin score (mRS) was calculated for each patient to assess the morbidity associated with the neurological involvement.

0	No symptoms
1	Some symptoms but not interfering with the normal functionality
2	Slight disability: Able to take care of themselves but unable to continue the previous routine
3	Moderate disability: Needs some assistance to do some tasks. Can walk unassisted
4	Moderate to severe disability: Unable to attend to own bodily needs or unable to walk, without assistance
5	Severe disability: Bedridden, incontinent, needs constant nursing care and attention
6	Dead

Table 2. Modified Rankin Score (mRS) to assess disability.

Ultrasound abdomen was done to rule out polycystic kidney disease associated with berry aneurysm. Due to limited resources, digital subtraction angiography (DSA) could not be performed within 48 hours of onset of meningitic symptoms. CT angiography was performed later during the hospital stay to rule out aneurysm and plan neurosurgical intervention. Additionally, in critical condition, the patients were not subjected to detailed investigations. The lifesaving investigations and interventions were prioritized.

Data Analysis:

The results are tabulated and presented in the form of figures and graphs for better illustration. Statistical Analysis was performed using Statistical Package for Social Sciences Version 25 (SPSS v25). The Quantitative data analysis e.g., Age, symptomatology, comorbidities etc., of the patients was done by means and 95% confidence interval. The Qualitative data analysis has variable outcomes e.g., Gender of the patient, lab results, physical evaluation, etc. were calculated by percentages and frequencies. The significance of value was determined at $P < 0.05$ and two-tailed level at 95% Confidence interval.

RESULTS:

In about two and half years of covid 19 pandemic (Dec 2019-August 2022), a total of 563 patients of pediatric age group were admitted in the intensive care unit with respiratory compromise necessitating mechanical ventilation, starting from 27th Feb 2020 to 26th Aug 2022. Out of total these 563 patients, 48 (8.5%, 95% CI [2.43-4.95]) patients were admitted in the intensive care unit for mechanical ventilation and later developed spontaneous subarachnoid hemorrhage of varies degrees.

Main neurological symptoms	Age Groups			95% Confidence Interval (95% CI)		Mean	Percentage
	1-5 years n=12	6-10 years n=9	11-14 years n=27	Upper Limit	Lower Limit		
Headache	4	9	25	23.7	26.8	0.79	79%
Dizziness	10	9	27	8.7	27.3	0.96	96%
Loss of smell	3	8	26	3.4	26.4	0.77	77%
Loss of taste	4	9	26	3.8	25.7	0.81	81%
Generalized Muscular Pains	3	7	27	3.2	27.2	0.77	77%
Seizure	4	2	9	3.6	9.1	0.31	31%
High grade fever	10	7	24	9.8	24.5	0.85	85%
Respiratory distress	12	9	27	8.6	27.3	1.00	100%
Cough	11	9	25	9.5	25.4	0.94	94%
Weakness	12	9	27	9.7	27.3	1.00	100%
Sudden loss of consciousness	5	6	11	4.6	11.2	0.46	46%
Comorbidities							
Multiple sclerosis	0	1	2	1.4	2.4	0.06	6%
Cerebral Palsy	5	1	2	1.3	5.3	0.17	17%
Chronic kidney disease	0	1	1	0.92	1.1	0.04	4%
Chronic artery disease	0	1	1	0.95	1.2	0.04	4%
Malignancy	1	1	2	1.5	2.3	0.08	8%
Berry aneurysm	0	1	1	0.56	0.93	0.04	4%
Tuberculosis	0	1	1	1.1	2.1	0.04	4%
Primary hypertension	0	0	1	1.1	1.4	0.02	2%
Myasthenia Gravis	0	1	1	1.4	2.2	0.04	4%
Metabolic Disorder of Inborn	2	1	0	1.3	1.9	0.06	6%

Table 3. Frequency and 95% Confidence Interval of COVID 19 symptoms stratified into 3 age groups

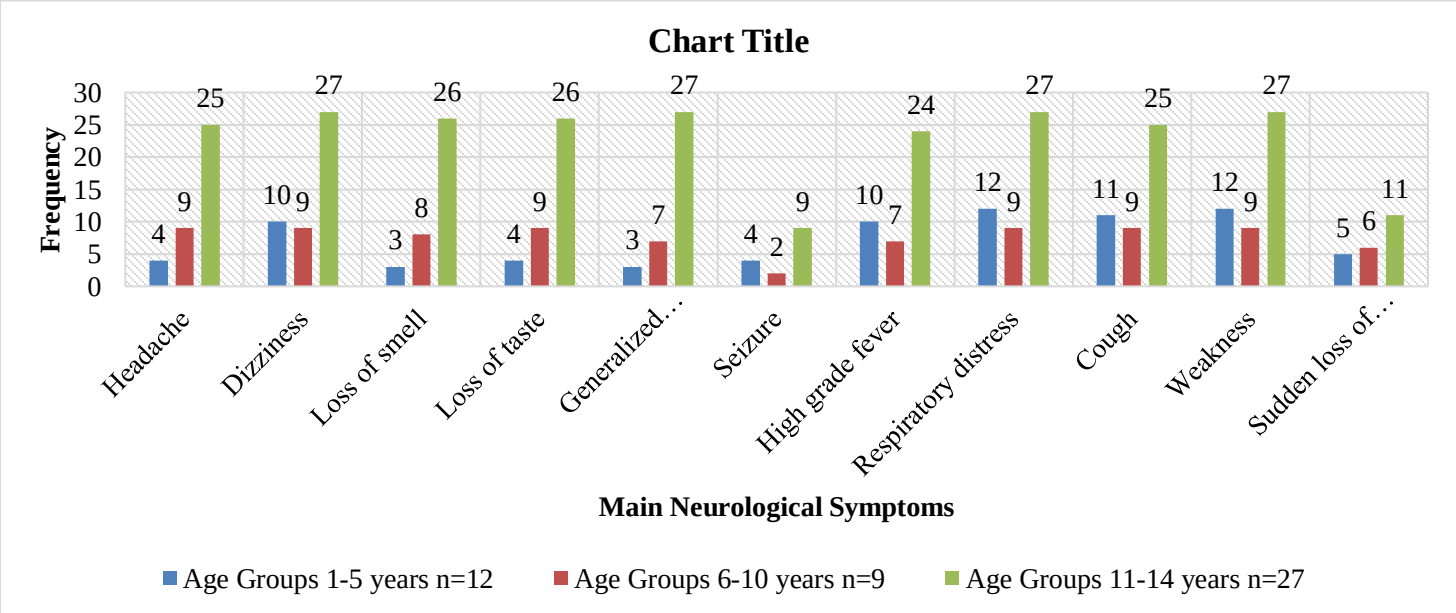


Fig.1. Elaborative illustration of frequency of main presenting complains in selected pediatric patients (from birth to 14 years of age)

The subjects of this study included 27 males (mean age=8.6 years, 95% CI 6.9-13.5) and 23 females. The subjects of this study included 27 males (mean age=8.6 years, 95% CI 6.9-13.5) and 23 females (mean age=7.9 years, 95% CI 7.4-13.2) showing male predominance with male to female ratio of 1.17:1. This predominance by a small margin was considered coincidental. (P < 0.98) An array of symptoms was recorded on detailed history that are encapsulated in Table 3, Fig.1. HRCT chest of all the patients was done showing that the ground glass infiltrates in bilateral lung field suggesting Covid 19 infection. However, the PCR of nasopharyngeal swab sample was taken as the confirmatory test and HRCT chest was significant in assessing the extent of lung pathology. The hematological analysis showed C-reactive protein, CRP (mean=231.3mg/L, 95% CI 198.2 mg/L-247mg/L), WBC count (mean=14.2 x 10^9/L, 95% CI 11.2 x 10^9-17.5 x 10^9), Platelet count (mean=245 x 10^9, 95% CI 210 x 10^9-265 x 10^9), activated partial thromboplastin clotting time (mean=49.2s, 95% CI 35.8s-42.2s), Prothrombin time (mean=13.2s, 95% CI 11.4s-14.2s), international normalized ratio (INR) mean=1.3, 95% CI 1.1-1.45), LDH levels (mean=490 U/L, 95% CI 476 U/L-546 U/L), and D-dimers (mean=760 ng/mL, 95% CI 740 ng/mL-782 ng/mL) (P < 0.037). According to the Fisher scale for the grading of subarachnoid hemorrhage, Grade 1 patients were n=23(48%), Grade 2 n=15(31%), Grade 3 n=7(14.5%), and grade 4 were n=3(6%). The descriptions of these grades are explained earlier in table 1. Twenty-nine of the total 48 patients (60%) had co-morbidities including Myasthenia Gravis 2 (4%), Multiple sclerosis 3 (6%), Cerebral Palsy 8 (17%), Berry aneurysm 2 (4%), chronic kidney disease 2 (4%), chronic artery disease 2 (4%), Malignancy 4 (8%), Tuberculosis 2 (4%), Primary hypertension 1 (2%), Metabolic error of newborn 3 (6%). The presence of comorbidities showed significant relation with the severity of covid infection and development of related complications such as subarachnoid hemorrhage (P < 0.027).

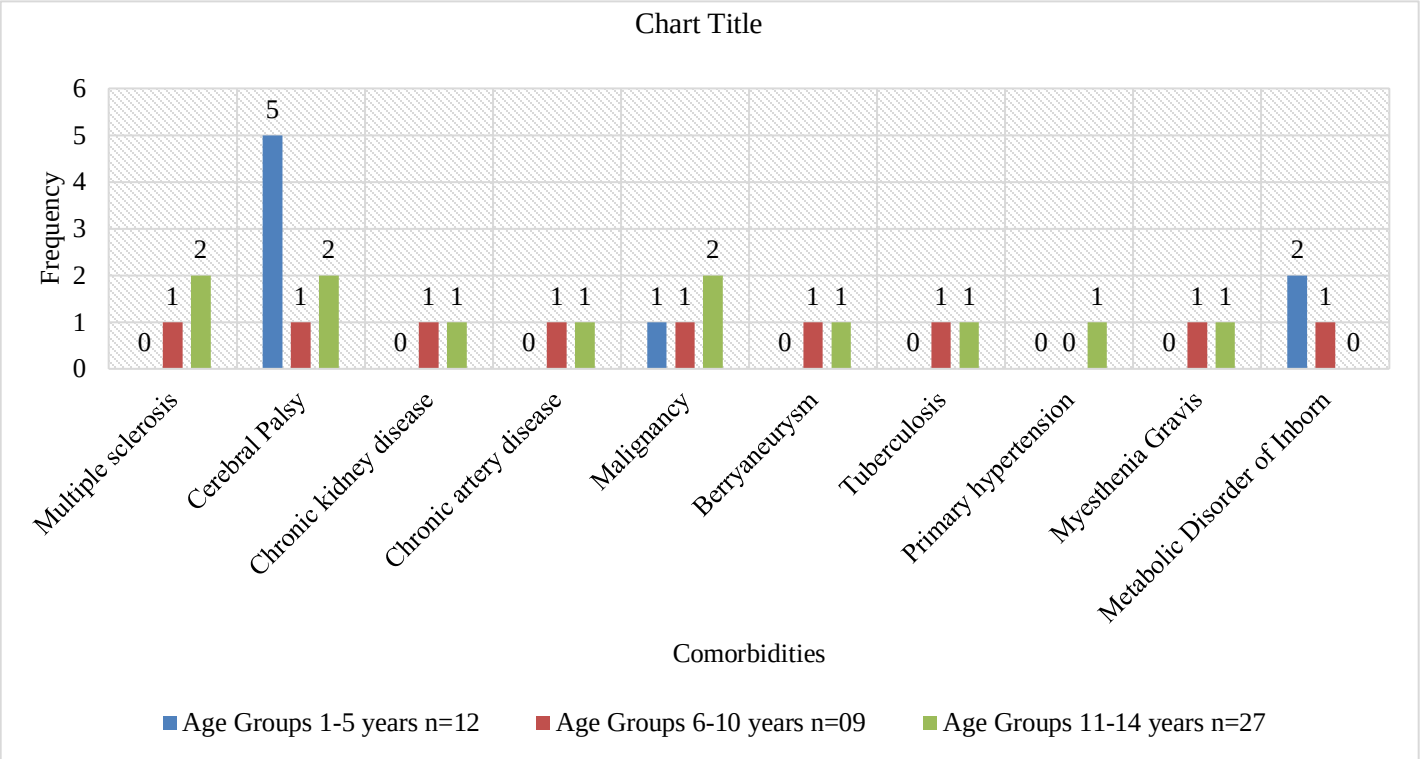
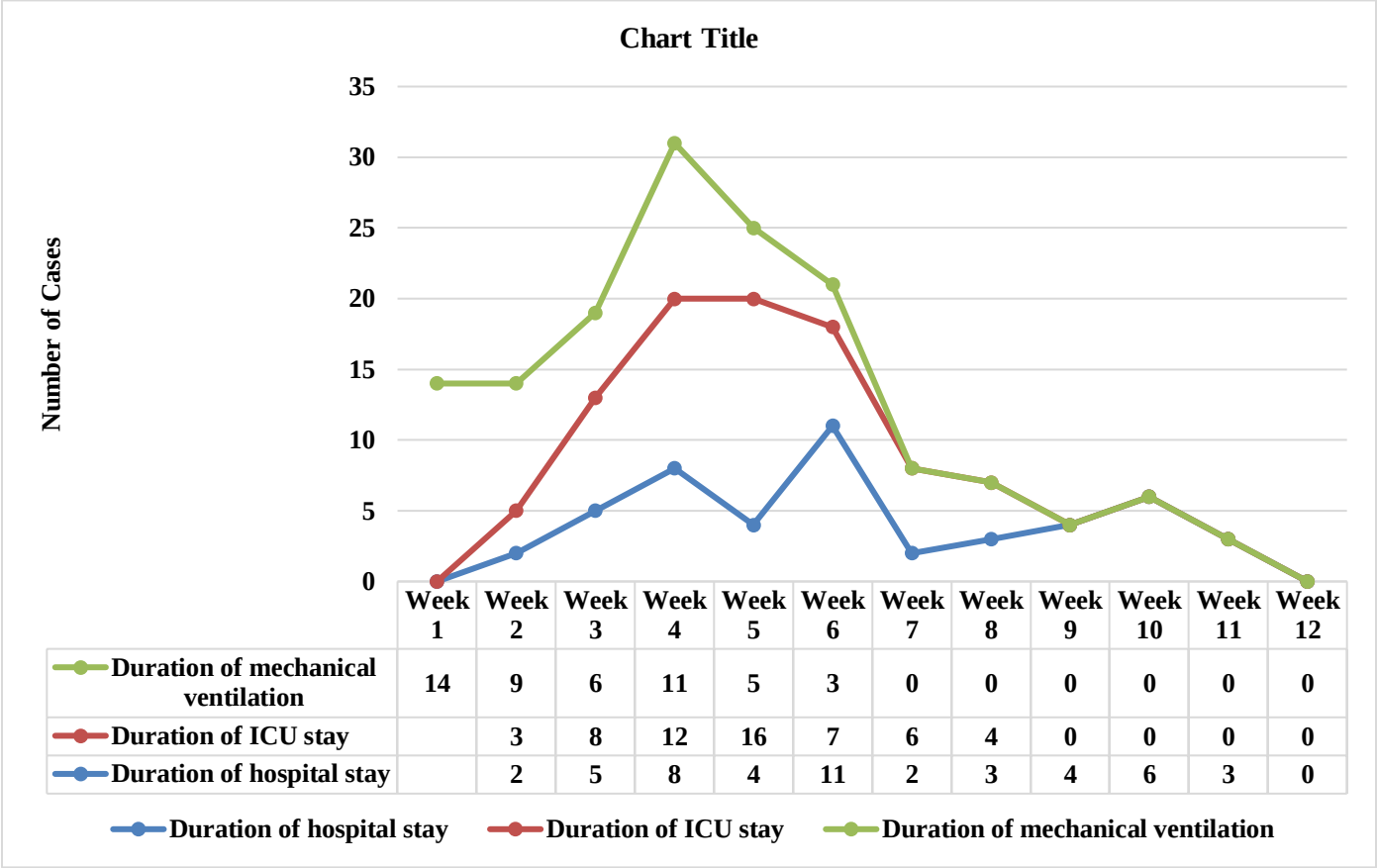


Fig.2. Frequency of comorbidities in selected subjects (n=48) in the different age groups (1-5 years, 6-10 years, 11-14 years)

In n=23, 48% of the cases, subarachnoid hemorrhage was undetectable on CT Brain plain however, non-traumatic lumber puncture report revealed xanthochromia, presence of radiologically occult subarachnoid hemorrhage. The WBC count in CSF analysis report ranged from 13.2 x 10^9 to 15.8 x 10^9

(mean=14.6 x 10^9) with neutrophil to lymphocyte ratio of 1.56:1.

At the time of discharge or end of hospital stay, the disability of the patients was assessed by modified Rankin Score (mRS). According to the data collected, 21(43.7%) patients had no symptoms after full treatment, 13(27%) patients had some symptoms, not interfering with normal functionality, 4(8%) retained slight disability, 2(4%) of the total patients had moderate disability, 1(2%) had moderate to severe disability, 2(4%) sustained severe disability, whereas 5(10%) patients expired during the course of hospital treatment (RR=0.19). Table 2. The range of duration of hospital stay was from 2 weeks to 11 weeks (average=6.8 weeks), duration of stay in ICU was 2 weeks to 8 weeks (average=5.7 weeks), and duration of stay on mechanical ventilation was 1 week to 6 weeks (average=3.5 weeks). The mortality of the patients showed no relation with the duration of hospital stay ($P > 2.195$). Likewise, the onset of subarachnoid hemorrhage showed no correlation with the onset of covid 19 symptoms ($P > 0.192$)



	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Duration of mechanical ventilation	14	9	6	11	5	3	0	0	0	0	0	0
Duration of ICU stay		3	8	12	16	7	6	4	0	0	0	0
Duration of hospital stay		2	5	8	4	11	2	3	4	6	3	0

Fig. 3. Showing the distribution of patients according to their duration of stay in hospital, ICU, and on mechanical ventilation during the acute episode of Covid 19 infection.

DISCUSSION:

This article highlighted the association between the COVID 19 infection and subarachnoid hemorrhage (SAH) in 48 patients during the era of pandemic. There was no significant gender predominance. The slightly high number of male patients was considered purely coincidental ($P < 0.98$). Patients of pediatric age group were included in the study with the mean age of 6.7 years-8.4 years. All the infants in this study had comorbidities. Almost all the infants were malnourished and were partially vaccinated to their age. According to the latest knowledge of COVID 19, comorbidities in early childhood make the patient more susceptible to developing COVID infection when exposed to it. The classical symptoms of acute viral respiratory tract infection including anosmia, generalized body aches and pain, cough, dyspnea, fever, weakness/dizziness etc. led to the provisional diagnosis of COVID 19 infection. The symptoms were more elaborate in children of age 10-14 years. [16] Probably because infants or young children who were not able to explain the subjective complaints could not add to the total data of symptomatology. In hematological investigations, the levels of inflammatory markers ESR, CRP, and LDH significantly correlate

with the severity of infection and its complications. [16, 17] In the background of COVID 19 associated endothelial dysfunction, patients with coexisting berry aneurysm were considered at high risk of developing spontaneous SAH. Two patients had berry aneurysm along with bilateral polycystic kidneys, which was noticed as an incidental finding. [18] The subarachnoid hemorrhage may occur as a consequence of anticoagulation therapy, but none of those 48 selected COVID-SAH patients were given anticoagulants amid COVID 19 infection. The coagulation profile of all the patients including platelet count, prothrombin time, INR, and APTT, was within normal range. So SAH in COVID 19 as a result of coagulation discrepancy is ruled out. [18, 19] Another possible reason for the spontaneous SAH in severe COVID 19 infection is mechanical ventilation. All the patients included in this study needed mechanical ventilation at some point during the hospital admission. In these COVID-SAH patients, the spontaneous SAH developed when the patient was on ventilator. Spontaneous hypocapnia on ventilatory support could be one of the reasons of developing spontaneous subarachnoid hemorrhage. COVID 19 infection primarily affects pulmonary system causing acute respiratory distress syndrome necessitating mechanical ventilation (MV) to compensate for respiratory compromise. This pathological process often leads to neurogenic pulmonary edema (NPE) linked with spontaneous subarachnoid hemorrhage. MV is essential in COVID 19 cases related to hypoxemia and hypercapnia, to improve blood oxygenation and prevent ischemic brain injury. However, hyperventilation can complicate brain autoregulation by excess carbon dioxide washout, risking the patient to develop brain injury. To avoid the MV related SAH, hypoxemia should be avoided, and permissive hypercapnia should be ensured to maintain the cerebral blood flow within the optimal limits. [17-20] Most of the patients fully recovered after the complete treatment and were discharged from the hospital. Their physical compatibility was assessed by using modified Rankin Score (mRS). This shows that with prompt management, permanent or long-lasting neurological compromise can be prevented. [21-23] In our study, the first 5 patients of COVID-SAH died and SAH was an incidental finding on postmortem. After getting the hint of this possible complication, whenever the GCS of COVID patient suddenly deteriorated, a detailed neurological examination to check for any neurological deficit/ Intracranial bleed was performed. The diagnosis was confirmed by CT brain plain and CSF analysis (Lumber puncture was performed after ruling out hydrocephalus). [24] Radiologically occult SAH was confirmed by non-traumatic LP and CSF analysis. The early detection of SAH is imperative and knowledge of this possible complication helped save lives. However, the exact mechanism of the disease progression is unknown. The occurrence of SAH can be early or late during COVID 19. The duration of COVID infection, hospital stay, and mechanical ventilation did not show any correlation with the onset of SAH ($P > 2.195$). [24, 25]

CONCLUSION:

Subarachnoid hemorrhage is a life-threatening complication of COVID 19 infection with high mortality rate all over the world. In our study, multiple factors and their association with subarachnoid hemorrhage were evaluated. In pediatric age group, the accurate neurological evaluation on MV support is difficult. However, early detection and prompt management of SAH-COVID 19 can remarkably improve the outcome. SAH in COVID patients was strongly related to the use of MV whereas, the duration of MV dependency had no impact on prognosis.

Limitations:

COVID 19 is not fading off the global canvas and it is here to stay for a while so complete knowledge of its pathology is required. According to the current literature review, our study is one of its kind to target COVID-SAH in pediatric age group at a relatively large scale, mainly covering the clinical aspect of the disease. However, extensive histopathological, biochemical, and molecular studies are required to identify the exact mechanism of SAH in COVID 19 infection for effective disease management.

Conflict of Interest: None

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