# **ASSESSMENT OF COGNITIVE FUNCTIONS IN COVID- 19 RECOVERED PATIENTS**

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### **"ASSESSMENT OF COGNITIVE FUNCTIONS IN COVID-19 RECOVERED**

### **PATIENTS"**

#### **DOCTOR OF MEDICINE**

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### **TABLE OF CONTENTS**



### **LIST OF FIGURES**





### **LIST OF TABLES**







#### **ABSTRACT**

**BACKGROUND:** The SARSCOV-2 is known to cause Microvascular and Macrovascular thrombotic phenomena in the vascular system, which has been found to increase the chances of blood clotting in the brain. Microvascular subclinical thrombotic phenomena that lead to impairment in cognitive functions have not been studied much in this pandemic. So this is the first kind of study. The study aims to determine whether this SARS CoV-2 produces cognitive impairment in the person who has suffered from COVID-19. If it produces cognitive impairment, then whether it persists even after one month or not or whether it resolves.

**MATERIALS AND METHODS:** This longitudinal prospective study was carried out after taking institutional Ethical committee clearance. People in the age group of 18 to 60 years who were diagnosed as COVID-19 Positive, and got recovered and discharged, were assessed at the time of discharge, after one month and after three months using cognitive assessment battery (PGI MEMORY SCALE, DSST, TMT, ADULT PROTEUS and MMSE).

**RESULTS:** A total of 205 subjects were included in the study.71% are males, and 28.3% are females. The majority that is 36% of the study population, is between 40-49 years. Parameters like TMT and PGI MEMORY have been statistically significant between discharge day, after one month, and three months follow-up. The age group of 40 to 48 years was most affected, with a frequency of 75%.

**CONCLUSIONS:** The study has shown that cognitive impairment can happen after COVID 19 disease.

**KEYWORDS:** Cognitive assessment, COVID-19,Microvascular thrombotic phenomena.

#### **INTRODUCTION:**

In December 2019, Novel Coronavirus 2, also known as Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), surfaced in the city of Wuhan, Hubei province in China 1 The infection caused by this virus is named Coronavirusdisease 2019(COVID-19) by WORLD HEALTH ORGANISATION(WHO)<sup>2</sup>

SARS COV -2 has a single-stranded RNA genome with 32 kilobases in length, considered the largest RNA virus genome. The frequency of recombination of RNA-positive strands is high.

If the host gets infected with multiple coronavirus strains, viral recombination occurs, creating problems in diagnosing the disease and vaccine production.

The transmission of the virus from person to person occurs via droplets<sup>3</sup> The manifestations of COVID -19 range from asymptomatic or mild or moderate to severe symptoms and even death. The symptoms include high-grade Fever, Flu-like symptoms like cold, cough, sore throat and shortness of breath 4 . Other symptoms are fatigue or 15eneralized weakness, malaise, respiratory distress, myalgia, loss of taste (Ageusia) and loss of smell (Anosmia). Some people may have severe symptoms like pneumonia and acute respiratory distress<sup>5</sup>. People with underlying comorbid conditions like hypertension, heart disease, chronic lung disease and Diabetes may show more severe symptoms<sup>6</sup>

### **AIM:**

 $\geq$  To assess the cognitive functions in COVID-19 recovered patients

### **OBJECTIVE OF THE STUDY:**

- ➢ To assess the cognitive functions in COVID-19 recovered patients.
- $\triangleright$  To see the delayed effect of the coronavirus on cognitive functions.
- $\geq$  To assess the progress of the cognitive changes over three months.

#### **REVIEW OF LITERATURE:**

Towards the end of 2019, cases of an unidentified Upper Respiratory Tract infection(URTI) began to appear in Wuhan, Hubei Province, China<sup>7</sup> Because medical professionals had no solutions or explanations for the illness's transmission or pathogenesis, it quickly spread throughout the city and, subsequently, the entire country. By the first half of January 2020, it was thought that the infectious disease was possibly caused by a novel coronavirus widely known as SARSCORONA VIRUS(severe acute respiratory syndrome coronavirus2; the condition was termed COVID-19 DISEASE (coronavirus disease 2019)<sup>89</sup>.

The virus quickly spread throughout the world, prompting the World Health Organization (WHO) to declare it a pandemic in early March 2020 10 . Lockdowns, constraints on travel, public transit, and meetings, as well as the closure of schools and businesses, were implemented to slow the spread<sup>11</sup>. All of these factors have hampered financial confidence, raising fears of a global recession.

#### **HISTORY:**

Humans have been recently infected by corona viruses, in contrast to viruses such as influenza, smallpox, and polio. When these viruses were discovered in the 1960s, there was little or nill pathogenic, epidemiological, or genetic information was available. All that was known was that they typically contain RNA encased in a membrane made up of spike-shaped protein structures  $^{12}$ .

The virus family was given the name after the crown-like appearances because of these surface spike molecules of protein ('corona' is the Latin word for crown)<sup>13</sup>. Viruses with that structural features are members of the Coronaviridae family, divided into four phylogenetic genera Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus <sup>14</sup> <sup>15</sup>

The Centers for Disease Control and Prevention (CDC) in the United States has now identified seven coronavirus strains that can infect humans. In general, they are single-stranded,

17

positive-sense RNA genome-bearing viruses. Their genome is estimated to be between 26 and 32 kilobases long (the human genome is 3 billion kilobases long)  $1617$ .

The very first coronaviruses discovered in humans were human CoV-229E and HCoV-OC43<sup>18</sup>. These viruses have been found to cause common URTIs like the common cold, and the infections they cause are mild. HCoV-HKU1 and HCoV-NL63, were discovered,after the discovery of first two strains<sup>19</sup>.

Other coronavirus strains found in humans include SARS-CORONAVIRUS, MERS-CORONAVIRUS, and SARS- CORONAVIRUS  $2^{16}$ . The above viral strains differ from the primary viral strains in that they end up causing potentially fatal infections and diseases. The extremely low R0 of HCoV-C43, HCoV-229E, HCoV-NL63, and HCoV-HKU1 distinguishes them from the serious coronavirus strains<sup>20</sup>. The basic replication number explains a pathogen's transmissibility or contagiousness<sup>21</sup>. Interventions like maintaining 2m distance and immunisation can impact the value, which is not fixed. R0 denotes the number of people who can be exposed to the virus by a single infected individual<sup>22</sup>.

Greater the R0 value,higher the probability to spread the infection. Organisms with R0 values greater than one are thus regarded as highly infectious. In contrast, organisms with low R0 values can be contained without isolating known cases and potentially contaminating people<sup>23</sup>. Even though these viruses have been present among humans for more than 60 years, they have only recently been at the forefront of research and media attention as a result of the SARS-CoV outbreak<sup>15</sup>, which previously was founded in the early  $20<sup>th</sup>$  century that this microorganism could cause a worldwide spread<sup>24</sup>. The most common 4 non-severe coronaviruses which can infect are found worldwide, though in lower concentrations in any given local population<sup>15</sup>. In accordance with the three severe coronavirus strains, SARS-CoV infections were concentrated in China, with relatively small epidemics in other countries. Since 2012, Middle East Respiratory Corona Virus are being reported, with most cases occurring in the Middle East.

The pathogen that causes COVID-19 DISEASE, SARSCORONA Virus, is a pandemic. SARS-CoV and MERS-CoV have been extensively studied and do not show any symptoms.

#### **SARS -COV:**

In November 2002, the SARSCORONA VIRUS first appeared in Guangdong Province, China. The strain is to blame for the SARS virus. Fever, fatigue, cough, and chills are all symptoms of an infection 25 . Many cases also experienced breathing difficulties and developed pneumonia<sup>25</sup>. Several people died from respiratory distress and lung failure<sup>26</sup>. Various factors, including pre-existing comorbidities and age, influenced patient outcomes. The SARSCORONA VIRUS incubation period was discovered to be 2-10 days<sup>26</sup>. It binds to the respiratory epithelial cells, causing major organ damage, primarily in the alveoli<sup>27</sup>. The virus is believed to originate in palm civet cats, implying a zoonotic spread to humans<sup>28</sup>.

#### **MERS-COV:**

In September 2012, a Betacoronavirus from Saudi Arabia became the  $2<sup>nd</sup>$  infectious agent in the human species<sup>30 31</sup>. With a mortality rate of 32-33%, this betacoronavirus strain is currently the most lethal<sup>15</sup>. MERS caused by this virus, MERS-CoV, has been reported in 27 countries, with Saudi Arabia accounting for 80% of these cases. There had been 2519 MERS cases as of January 2020, with 866 deaths<sup>32</sup>. MERS is believed to have begun in camels(dromedry) and infected to people through a zoonotic transmission<sup>33</sup>. In MERS, the time period between exposure and the appearance of the first symptom lasts about 5- 6 days, but symptoms can last anywhere ranging from two to fourteen days<sup>34</sup>. Symptoms include high grade fever, coughing, and breathing difficulties, in the most severe cases of viral infections.

#### **SARS-COV 2:**

On December 31, 2019, the WHO received the first report on COVID-19 DISEASE in Wuhan, China. In March 2020, the virus was announced as a worldwide pandemic. By the month of April 2020, the virus had infected 214 countries and was expanding rapidly (Fig.  $1<sup>3637</sup>$ . As with MERS and SARS, patients prognosis are influenced by variables like pre-existing comorbid conditions . According to Chinese officials, individuals over 80 have the highest mortality rate <sup>38</sup>.COVID-19 DISEASE has an incubation period of 14 days; throughout this time, the virus may infect others<sup>38</sup>. The virus can cause similar symptoms as that of MERS. And SARS, including symptoms such as fever, coughing, and breathing difficulties<sup>38 39</sup>. The basic reproduction number is 3 and 0.45 for SARS and MERS, respectively, and early COVID-19 DISEASE figures ranged from 2.2 - 3.11 31 40 <sup>41</sup> COVID-19 DISEASE has the same R0 as that of SARS but has a greater viral replication in patients' noses and throats before the appearance of signs and symptoms, whereas SARS has a connection which is more directly linked to symptoms<sup>41</sup>. This implies that this disease can spread before the appearance of symptoms<sup>42</sup>.



Fig. 1. Reported cases of COVID-19 by country adapted from CDC. Red represents China, the SARS-CoV-2 origin. Orange represents countries reporting COVID-19 cases. Green represents major countries reporting no cases of COVID-19 and includes Lesotho, North Korea, and Turkmenistan. Figure reproduced from [155].

#### **EPIDEMIOLOGY OF SARS CORONA VIRUS:**

In most(80%) cases, COVID-19 DISEASE symptoms include a low-grade fever, a dry cough, and difficulty breathing. In serious cases, 44% of patients experienced dyspnea (shortness of breath), 50% experienced hypoxia (oxygen depletion in body tissues), and 14% experienced a high fever <sup>43 44 45 46.</sup> Hospitalisation rates vary by age in the U.S. They tend to be from 0.1% in case of children aged (5-17) and 17.2% for people aged 85 and up, of these 5 percentage of cases which experienced severe conditions like septic shock and multiple organ dysfunction<sup>43</sup> 44 45 46 47

The two most important clinical symptoms that emerge in clinically ill COVID-19 DISEASE infected persons<sup>48</sup> are low oxygen levels due to ARDS and high fever<sup>49</sup>. This decrease in level of saturation of oxygen is treated with ventilator<sup>50</sup>. Furthermore, it is believed that later stages of COVID-19 DISEASE result in decreased oxygen saturation because of decreased lung compliance <sup>50 51 52 53</sup>. Those asymptomatic but infected with COVID-19 DISEASE can still spread the disease<sup>54</sup>.

COVID-19 DISEASE has insisted intense precautionary measures be practised to reduce spreading and morbidity. This aims to 'flatten the curve' of the projected infection rate and prevent healthcare services from becoming overburdened with so many new cases at once. According to some models, social distancing ( keeping a 2 m distance) would decrease the estimated infections by 78%<sup>55 56</sup>. Furthermore, the criticality of disease and onset of COVID-19 disease vary drastically with age, with the symptoms worsening along with increased age 57 . Those individuals whose age fall below 19 are at the least risk, with mortality rates ranging from 0% to 0.1%, while those between the ages of 75 and 84 face mortality rates varying from 4.3% to 10.5%. Those aged 85 and up are the most vulnerable, with mortality rates tending to range from 10.4 to 27.3%<sup>57</sup>. Diabetes, cardiovascular disease, and immune system suppression contribute to an increased mortality rate 58 .

SARSCORONA Virus, like other coronaviruses, is a positive sense RNA virus with a single strand that binds to epithelial cells of lungs via spike proteins (Fig. two)<sup>59</sup>. Receptor binding region of virus, the receptor of ACE2 (Fig. 3), are identical to the virus<sup>60</sup>. These receptors serve as SARSCORONA VIRUSspike protein docking sites, permitting virus and cell membranes to merge (Fig. 3). Then the cells are controlled by the virus by incorporating its Ribosnucleic acid into the replication system of the cells and which allows the spread of virus. Thus virus can spread to the entire body, inducing immune system responses and infecting the individual<sup>61 62</sup>







Figure 3 Diagram of SARS COV2 Virus Entry into host cell

Coronaviruses bind to host cell receptors via their homotrimeric spike glycoprotein (S protein) (Fig.  $3$ )<sup>63</sup>. At the time of infection, the protein S is cleaved into S1 and S2 subunit. The first subunit(S1) consists of two RBD (receptor binding domain)which allows the virus to cling to the host cell, and the function of the second  $(S2)$  subunit is to merge the membrane<sup>64</sup>.

ACE2 is the host cell receptor for S1 subunit of Protein S, an Integral polytopic protein found on epithelial cells of the heart, lungs and kidneys<sup>65</sup>. Transformation is the main physiological

function of the angiotensin, which plays a role in blood pressure and constriction of vessels<sup>66</sup>. The ACE2's anti inflammatory expression safeguard against lung damage. In contrast, SARS-CoV or SARSCORONA VIRUS binding leads to increased pro-inflammatory markers that induce severe lung damage<sup>67 68</sup>. This receptor is significantly related to the transmissibility and infectivity of the SARSCORONA VIRUS, in addition to its potential role in COVID-19 pathology.

The SARS-CoV-2 RBD region has a 10-20-fold higher binding affinity to the ACE2 receptor due to differences in the sequence of amino acids allowing the more communications of protein S and the receptor of cell  $69\,70$  Virus's capacity to bind for ACE 2 receptors on host cells also helps determines the transition of host organisms through which these can spread the disease before transmitting to humans, and thus how organisms can be studied<sup>71 72</sup>. When S1 subunit binds to the ACE2 receptor on target cell, then the S2 's heptad repeat 1 (HR1) and 2 (HR2) sites join together and form helix that which brings the virus and host cell walls together and gets merged<sup> $72\,73$ </sup>. When the membranes fuse, the coronavirus RNA enters the cell into the cytoplasm via initial endosome, where it get transcribed into a translation complex, which then converts subgenomic RNA to structural and accessory proteins (Fig.  $3^{74.75.76}$ . These proteins bind together to form viral particles, which are sent out of the cell and transmit the virus to nearby cells, enabling the disease to spread all through the organism.

#### **MECHANISM OF TRANSMISSION OF INFECTION:**

The viral transmission is mainly between infected hosts through contact with viral particlecontaining droplets<sup>76</sup>. Droplets (coughs, sneezes, and mucous) can't travel not more than two meters from source $^{77,78}$ .

It is widely assumed that the droplets don't stay in air.In a study discovered that droplets lingering in the air for three hours<sup>78</sup>. Disease can also be transmitted by potentially infectious objects (fomite-mediated transmission). Surfaces on cardboard were infectious for several hours, and surfaces on plastics and stainless steel were infectious for up to three days<sup>78</sup>.

#### **TESTING FOR VIRUSES:**

Currently,"Quantitative reverse transcription-polymerase chain reaction  $(RT-qPCR)$ " <sup>79</sup> is the most common type of testing. It is broadly used in countries such as Hong Kong, the united states, Italy, Germany, and South Korea to counteract the pandemic<sup>81 82 83</sup>. A nasopharyngeal swab is used in the test to collect genetic information that will disclose whether the patient is infected with virus. Testing necessitates RNA seggregation, followed by synthesising a complementary DNA<sup>83 84 85</sup>.

Antibody tests are available from companies such as Abbott<sup>85 86</sup>. Serological tests are far more successful, with Abbott and Swiss comapnies claiming success rates of more than 99%ELISA testing is another viable option due to its sensitivity<sup>87</sup>. Some of the early pandemic serological assays, however gives false positive results and overestimation of infection rates<sup>88</sup> 89.

# **MANIFESTATIONS AND MECHANISMS OF SARS CORONA VIRUS-INDUCED CENTRAL NERVOUS SYSTEM DAMAGE:**

Respiratory symptoms range in severity from mild to severe, and the illness can advance from mild to life-threatening severe form i,e Acute respiratory distress syndrome (ARDS. Individuals who are severely affected are more susceptible to neurological problems ranging from nausea and headaches or giddiness to more serious seizures and cerebrovascular disease (CVD). Autopsy reports on patients with severe disease revealed cerebral fluid retention and neurological degeneration . Furthermore, acute seizures in two patients with severe COVID-19 DISEASE have been reported, inferring that COVID-19 DISEASE may end up causing CNS damage. A virus comparison showed that amino acid substitutions in SARSCORONA VIRUS were responsible for functional and pathogenic differences. The SARSCORONA VIRUS spreads through the respiratory tract, the Gastro Intestinal(GI) tract, and aerosols. It infiltrates human cells by binding to the ACE2 protein, which is found in airway epithelium, renal cells, lung parenchyma, cardiovascular and gastrointestinal systems, but not the central nervous system<sup>90 91 92</sup>. According to neurological research<sup>93</sup>, ACE2 is primarily expressed in the cortex, but also in microglia and neuronal cells in the brain<sup>94</sup>.

These findings imply that ACE2 expression is related to SARS CoV-2's neurotropic potential<sup>95</sup>. SARSCORONA VIRUS neuroinvasion implies that the virus can invade the respiratory tract to the Central nervous system and cause harm either directly or indirectly via the host's immune response. By infecting Blood Brain Barrier (BBB) endothelial cells or binding to the endothelial protein ACE2, SARSCORONA VIRUS can also enter the Central Nervous System (CNS). The SARSCORONA VIRUS cytokine storm may also degrade the BBB, raising permeability and allowing entry of pathogens into the Central nervous system via infected immune cells.

As a result, neuropathological correlates of SARSCORONA VIRUS disease include hypoxemic encephalitis, demyelinating disorders, cerebrovascular disease, acute myelitis, and others. These are due to spurious immune system reaction leading to secondary inflammatory tissue injury<sup>96</sup>.



Figure 4 – Mechanism underlying SARS COV 2 Damage to CNS



Figure 5- Mechanism underlying SARS COV 2 Damage to CNS:- Blood borne and immune pathways.



Figure 6- Mechanism underlying SARS COV 2 damage to CNS, Direct infection route.

#### **MANIFESTATIONS OF NERVE DAMAGE CAUSED BY SARS COV-2:**

Fever, cough, pneumonia, multiple organ dysfunction, and pneumonia are all clinical manifestations of SARSCORONA VIRUSinfections. In a COVID-19 DISEASE patient study conducted in Wuhan, China, 36% that is 78 out of 214 patients noted CNS manifestations such as drowsiness, and changes in mental status<sup>49 97</sup>. In addition, some patients had epilepsy, CVD, and consciousness issues, epilepsy<sup>98</sup>. The clinical picture of SARSCORONA virus-induced nervous system injury include encephalitis, olfactory and gustatory disorders, encephalitis, and metabolic toxic encephalopathy.

COVID-19 patients experience a high rate of headaches<sup>99</sup>. A systematic study and evaluation of 138 admitted to a hospital with COVID-19 revealed headache and dizziness incidence rates of  $6.5{\text -}8.0\%$ <sup>100 101</sup>. There is no known pathological correlation between headaches and COVID-19. Headaches can be probably caused by inflammatory response in the central nervous system caused by chemicals released by nociceptors; thus, the underlying pathophysiology of headaches in COVID-19 patients could involve chemokines and cytokines released by macrophages<sup>102</sup>.

In a survey of COVID-19 patients in Spain, 57% (483/841) reported various levels of neurological problems, with severe headaches and dizziness reported early on<sup>102</sup>.

Clinical manifestations of COVID-19 include olfactory and gustatory disorders, with a few studies indicating a potential connection among olfactory abnormalities and COVID-19 severity . A analysis of 72 COVID-19 people with the disease discovered that they all suffered from differing extents of olfactory and gustatory abnormalities<sup>99</sup>. While mild respiratory symptoms are common in children with COVID-19, there have also been studies of children with olfactory and gustatory abnormalities<sup>99 103</sup>.

A recent study of three COVID-19 patients who developed encephalitis or encephalopathy reported that their cerebrospinal fluid analysis revealed elevated anti-S1 IgM

28

levels, as well as significant increases in the interleukins IL-6, IL-8, and IL-10. Still, the virus was not detected in the cerebrospinal fluid $104 105 106$ .

―Five patients in New York aged <50 years were diagnosed with COVID-19 and presented with new-onset symptoms of large-vessel ischaemic stroke between March 23 and April 7, 2020; the average National Institutes of Health Stroke Scale score was 17 points(range: 0-42 points) 107,108,109,110

Plasminogen levels are elevated in COVID-19 patients; plasminogen-related hyperfibrinolysis can raise D-dimer levels in critically ill patients and is frequently complicated by coagulopathy and vascular endothelial cell dysfunction<sup>111 112</sup>. Critically ill COVID-19 patients are more likely to experience acute cerebrovascular events, which may be associated with severe thrombocytopenia and elevated D-dimer level<sup>113,114,115</sup>.

#### **Mechanisms underlying SARS-CoV-2-induced nerve damage:**

Viruses can enter the CNS via axonal transport mechanisms by infecting peripheral neurons<sup>116, 117</sup>. Viruses can infect sensory or motor nerve endings and travel retrograde or anterogradely<sup>118,119</sup>. SARS-CoV-2 is primarily transmitted through the nasal respiratory tract. According to research, olfactory bulb ablation can limit coronavirus invasion of the CNS<sup>120121</sup>. This suggests that many viruses enter the CNS via the olfactory nerve and olfactory bulb<sup>122</sup>. According to a recent study, the SARS-CoV-2 virus was found in the olfactory neurons of COVID-19 patients<sup>123</sup>. These findings suggest that coronaviruses can enter the CNS via retrograde neuronal transmission.

―Viruses can enter the CNS and other locations by infecting leukocytes or blood-brain barrier endothelial cells<sup>116 124</sup>. Vascular endothelial cells, astrocytes, pericytes, and the extracellular matrix make up the blood-brain barrier. Because all vascular endothelial cells express ACE2, SARS-CoV-2 can enter the CNS by binding to this membrane-bound enzyme

on blood-brain barrier capillary endothelial cells 95 . Viruses can also cross the blood-brain barrier by infecting peripheral leukocytes, which enter the CNS via blood circulation. SARS-CoV-2-induced systemic inflammatory cytokines, chemokines, and other soluble mediators may also damage the blood-brain barrier, increasing its permeability and thus allowing viruses and infected cells to enter".

Antiviral immune responses are critical for pathogen removal from the body. The cytokine storm caused by an excessive and abnormal host immune response, on the other hand, can cause systemic inflammatory response syndrome. Increased levels of inflammatory cytokines can also lead to cognitive decline<sup>125</sup>. SARS-CoV-2 infection of respiratory epithelial cells, dendritic cells, and macrophages cause the release of antiviral factors (interferons), proinflammatory cytokines (IL-1, IL-6, and TNF), and chemokines. Another study found that severely ill patients had significantly higher levels of serum granulocyte colony-stimulatory factor (GCSF), IP-10, monocyte chemoattractant protein (MCP) 1, macrophage inflammatory protein (MIP) 1, and TNF- when compared to mildly ill patients. These studies suggest a link between cytokine storms and disease severity<sup>49</sup>. Viral replication can cause apoptosis in epithelial and endothelial cells, as well as vascular leakage, resulting in the release of proinflammatory cytokines and chemokine<sup>126</sup>. Critically ill patients frequently have elevated IL-6 and IL-8 levels, as well as lower lymphocyte counts, particularly for CD4- and CD8-positive cells, which can predict disease characteristics and progression. IL-6 is required for the impairment of immune cytotoxic functions<sup>127</sup> additionally, IL-6 may serve as a biomarker for early detection of COVID-19 progression <sup>128</sup> <sup>129</sup>

"The activation of immune cells and the increase of inflammatory factors may cause chronic inflammation of the brain and CNS complications. Moreover, tocilizumab (an IL-6 receptor blocker) can control the COVID-19-induced cytokine storm to a certain extent. Immune cell activation can cause chronic inflammation and nerve damage in the brain. These results show that SARS-CoV-2 can trigger cytokine storms and neuro-inflammatory responses by activating mast cells, neurons, glial cells, and endothelial cells<sup>130</sup>. In SARS-CoV-2 patients, pulmonary inflammation can impair gas exchange, resulting in hypoxia in the CNS, followed by cerebral vasodilation and interstitial oedema". COVID-19 patients may develop venous or arterial thromboembolism as a result of inflammation and hypoxia, which can lead to complications such as ischaemic stroke, myocardial infarction, and pulmonary embolism<sup>131 132</sup> COVID-19 patients may develop coagulopathies caused by cytokine storms or sepsis, which can lead to stroke 133

Sepsis-induced coagulopathy is a precursor to disseminated intravascular coagulation, which can cause prothrombin time prolongation, elevated D-dimer levels, and thrombocytopenia, followed by endothelial dysfunction and micro thrombosis<sup>134</sup>.

ACE2 is a key component of the renin-angiotensin-aldosterone system. It is found throughout the body and CNS because it is widely expressed in the human lung parenchyma, airway epithelium, kidneys, small intestine, and vascular endothelial cells<sup>117</sup>. ACE2 counteracts the effects of ACE1 and angiotensin-II, providing cardiovascular protection. Because the spike protein of SARS-CoV-2 has a high affinity for ACE2, ACE2 is an important target for vaccine and antibody development<sup>69</sup>. SARS-high CoV-2's pathogenicity is due to its strong affinity for the human ACE2 protein<sup>138</sup>

Previous research has found ACE2 activity in human cerebrospinal fluid; a recent immunocytochemistry study using mixed neurons derived from human pluripotent stem cells discovered high ACE2 expression in neuronal cell bodies but low expression in axons and dendrites<sup>139</sup>. Although this study did not use human brain tissue, it does show that ACE2 is expressed in neurons, making neurons a potential target for SARS-CoV-2. SARS-CoV-2 infected a mouse model expressing human ACE2 protein, resulting in high viral loads in the lungs, trachea, and brain<sup>140</sup>. SARS-CoV-2 binding to ACE2 may cause abnormally high blood

31

pressure, increasing the risk of a cerebral haemorrhage. Because ACE inhibitors increase ACE2 expression, future research could look into whether patients with hypertension and Diabetes who use ACE inhibitors are more vulnerable to  $SARS-CoV-2$  infection<sup>141</sup>. Despite the fact that several countries are actively working to develop antiviral drugs and vaccines, long-term nervous system sequelae caused by SARS-CoV-2 are gaining increasing attention<sup>142 143 144</sup>. Within six months of discharge, 509 of 797 patients had sequelae. Neurological sequelae accounted for 20.8%<sup>145 146</sup>. A prospective, multicenter cohort study of 73197 hospitalised COVID-19 patients in the United Kingdom from January 17 to August 4, 2020, discovered that 4.3% (3115 patients) seemed to have neurological complications<sup>147</sup>

SARS-COV-2 injury to neurons, whether direct or indirect, has been shown in studies to cause mental disorders and nervous system cognitive impairment<sup>148 149 150</sup>. The MRI of 51 COVID-19 patients taken three months after discharge was analysed<sup>150</sup>, and severe patients appeared to have indirect brain damage related to inflammatory factors (e.g., CRP, procalcitonin, and IL-6), particularly in the thickness of the cerebral cortex; reduced cerebral blood flow and white matter microstructure changes are more serious, causing structural changes in brain volume, blood flow, and white matter microstructure.

More research is needed to address the issue of cognitive impairment<sup>151</sup>. COVID-19 survivors are primarily tormented by fatigue or muscle weakness, sleep difficulties, and anxiety or depression six months after acute infection and these are the primary targets of long-term rehabilitation intervention<sup>152</sup>. Furthermore, studies have shown that approximately 30% of COVID-19 patients have persistent olfactory dysfunction 152 . A follow-up survey of 55 COVID-19 patients who lost their sense of smell between the end of February and early march 2020 discovered that 91% of the patients regained their sense of smell after eight months, with 53% fully recovered<sup>153</sup> Patients with pre-existing neurological diseases are more vulnerable to

COVID-19 infection. Patients with Alzheimer's and dementia are at a greater risk of severe COVID-19 infection and neuropsychiatric disorders.

In cerebral vascular endothelial cells, ACE2 is widely expressed. The high bonding of SARS-CoV-2 spike glycoprotein for ACE2 can cause varying degrees of damage to the bloodbrain barrier 154 . Furthermore, cytokine storms, hypoxia, and coagulopathy can compromise the integrity of the blood-brain barrier. These combinations could be the source of long-term nervous system sequelae<sup>155</sup>.

Systemic inflammation has been linked to cognitive decline and neurodegenerative diseases, which may lead to neurodegeneration in COVID-19 patients in the coming years<sup>156</sup>. COVID-19 patients are likely to have NLRP3 inflammation activation<sup>155</sup>, which can straightforwardly induce or worsen the neurodegenerative process that leads to Alzheimer's diseases<sup>155</sup>. Furthermore, NLRP3-driven and IL-1-mediated phosphokinase and phosphatase regulation play a significant role in the pathological deposition of neurofibrillary tangles, which may induce or aggravate neurodegeneration in COVID-19 patient<sup>157</sup>. According to research, the ACE2 protein is up-regulated in the brains of Alzheimer's disease patients, and there is a substantial positive correlation between ACE2 protein expression and oxidative stress<sup>158</sup>. This could be one of the factors contributing to the SARS-CoV-2 virus's long-term nervous system sequelae.

According to Ministry of Health and Family welfare by Government of India data states that there are 5 lakhs Death happened till October 2022 where as according to the World Health Organisation (WHO) cumulative deaths are 66 lakhs .

33



Figure 7- Thrombo Embolisim Involving Different Systems

### **MATERIALS AND METHODS:**

#### **SOURCE OF DATA:**

Subjects who have been diagnosed as COVID-19 positive and got recovered are included in the study after taking informed consent at Shri B.M. Patil Medical College, Hospital and Research Centre, BLDE (DEEMED TO BE UNIVERSITY), Vijayapura, between November 2020 to October 2022.

### **METHOD OF COLLECTION OF DATA:**

#### **1. STUDY POPULATION:**

This study was done in Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, from November 2020 to November 2022 in individuals who have recovered from COVID-19.

### **2. INCLUSION CRITERIA:**

- People in the age group of 18 to 60 years who were diagnosed as COVID-19 Positive, got admitted at Shri B. M Patil Medical College, Hospital and Research Center, BLDE (DU), and got recovered and discharged, were interviewed at the time of discharge, after one month and after three months.
- Subjects willing to consent.

#### **3. EXCLUSION CRITERIA:**

- Any patients with a Pre-existing mental illness or cognitive impairment or patient with mental retardation.
- Previous history of Stroke.



### **METHODOLOGY:**

### **SAMPLE SIZE**

With the anticipated Mean $\pm$ SD of the Sign coding test among after recovery of COVID-19 patients 31.14±9.02 (8) , the study would require a sample size of 81 patients with a 95**%** level of confidence and a precision of 2**.**

Formula used

•  $n = \underline{z^2} S^2$ 

**d 2**

Where  $Z = Z$  statistic at  $\alpha$  level of significance

 $d^2$ = Absolute error

### **S= Standard deviation**

 $q= 100-p$ 

Dropout rate  $=10\%$  of 81

Sample size=Minimum 90

### **STATISTICAL ANALYSIS:**

- The data obtained will be entered into a Microsoft Excel sheet, and statistical analysis will be performed using a statistical package for the social sciences (Version 20).
- Results will be presented as Mean (Median)  $\pm SD$ , counts and percentages and diagrams.
- For not normally distributed variables Friedman test.ll be used. Categorical variables will be compared using the Chi-square test.
- p<0.05 will be considered statistically significant. All statistical tests will perform two-tailed.

**TYPE OF STUDY**: Prospective longitudinal study

#### **COGNITIVE ASSESSMENT:**

Assessment of cognitive functions is done by using the Neuropsychological tests

#### **NEUROPSYCHOLOGICAL TESTS**

#### **TRAIL MAKING TEST (TMT):**

Trails A and B are timed validated assessments of complex attention. Part A of the Trails Making Test comprises of 25 circles on a sheet of paper with numbers 1-25 written in random locations. The subject must link the circles in numerical order as as fast as possible in less than 90 seconds. Part B of the Trails Making Test comprises of 25 circles on a sheet of paper with numbers 1-13 and letters A-L written in random locations. It necessitates the subject to link the circles as as fast as possible in numerical and alphabetical order, alternating among numbers and letters in less than 180 seconds. With a pencil, the trails are finalised on worksheets.This tests visual scanning and visuomotor tracking,which measure the speed of processing measured in seconds.

#### **DIGIT-SYMBOL SUBSTITUTION TEST(DSST):**

A timed neuropsychiatric test sensitive to onset of dementia is digit-symbol substitution. It consists of a top-of-the-page key of nine digit-symbol pairs, preceded by rows of digits below missing symbols. It necessitates the subject to match symbols to digits as quickly as possible using the provided key. The number of correct symbols within 120 seconds is tallied. The test is completed with a pencil on a worksheet.

The DSST assesses a variety of cognitive operations. To perform well on the DSST, you must have good motor speed, attention, and visuoperceptual functions, including the ability to scan and write or draw (ie, basic manual dexterity). Associative learning may also have an impact on performance. For example, if pairings are quickly learned after the first few trials, the subject's performance speed will improve because he or she will no longer have to refer to the key to verify the correctness of each pairing. The conscious decision to use this learning strategy to improve performance speed necessitates the executive functions of planning and

strategizing. Working memory, another executive function, is likely required to remember task rules and to keep required symbol digit pairs up to date.

#### **P.G.I.MEMORY SCALE(PGIMS):**

―It defines memory as the ability to retain and reproduce impression's once perceived intentionally. It includes verbal and non-verbal material and measures remote, recent and immediate, short-term, very short-term, intermediate-term and long-term memories. There are ten subtests, standardized on adult subjects in the age range of 20 to 45 years. Its test-retest reliability over a period of one week ranges from 0.69 to 0.85 for ten subtests ( $N = 40$ ) and for the total test about 0.90 (test-retest and split-half). The correlation of PGIMS with Boston's Memory Scale and Wechsler's Memory Scale were found to be 0.71 and 0.85, respectively. Elderly subjects obtained significantly lower scores than the younger subjects. Cases suffering from organic brain pathology and functional psychotic conditions obtained significantly lower scores than normals and neurotics." It has satisfactory cross-validity and provides quintile norms and a profile. Scores of the subjects suffering from organic brain pathology, functional psychosis and neurosis fall in the lowest, 2nd and middle quintiles, respectively. Thus the result showed that the PGI Memory scale is a satisfactorily reliable and valid tool to measure memory in the clinic population. (Pershad, 1977; Pershad and Wig, 1976, 1988).

In our study we used PGIMS because it is designed to Indian population and more over it is present in regional language which is more easy to apply to the Indian population.

#### **MINI-MENTAL STATE EXAMINATION (MMSE):**

Folstein developed the Mini-Mental State Examination (MMSE) or Folstein test in 1975. It is a 30-point questionnaire used extensively in research and clinical settings to measure cognitive impairment. It is commonly used to screen for onset of dementia. It is also used to predict the severity and progression of cognitive impairment and to track an individual's cognitive changes over time, making it an efficient method to document an individual's response to treatment.

39

#### **PORTEUS MAZE TEST (PMT):**

The Porteus Maze test (PMT) is a type of psychological assessment. Its purpose is to assess psychological planning ability and foresight. It is a nonverbal intelligence test. Stanley Porteus, a psychology professor at the University of Hawaii, created it.

The subject must solve a series of mazes as part of the test. The mazes vary in difficulty. The test lasts 15-60 minutes and allows the subject to complete as many as mazes feasible. The test is used as a supplement to the Wechsler intelligence scales.

### **RESULTS**

### **AGE DISTRIBUTION:**

It was observed that the majority of the patients (36.6% ) belonged to the age groups of 40 to 49, followed by (32.7%) belonging to the age group 50 to 60 years. The remaining (22.9%) belonged to the age group 30 to 39 years.

Age (YEARS)	<u>2001 18 announce</u> paintenais accounting to age. <b>Number of Cases</b>	Percentage of cases
< 20	1	0.5
$20 - 29$	15	7.3
$30 - 39$	47	22.9
$40 - 49$	75	36.6
$50 - 60$	67	32.7
Total	205	100.0

**TABLE 1: Distribution of patients according to age:**

### **Graphical Representation 1: Distribution of patients according to age:**


# **GENDER DISTRIBUTION:**

It was observed that the majority were males, with 71.7% of patients(147 in number), while 28.3% of subjects were females (28 in number).

# **Table 2:Distribution of patients according to Gender:**



# **Graphical Representation 2: Distribution of patients according to Gender:**



#### **PSYCHOLOGICAL ASSESSMENTS:**

#### **1. Trail Making Test -A (TMT-A):**

In this Trail making test-A(TMT-A), we observed that the average time taken on discharge is 25.0 seconds, after one month is 25.42 seconds, and after three months is 25.55 seconds. The difference in means from the day of discharge to after one month and after three months is 0.42 seconds and 0.55 seconds, respectively, which suggests that there is a subtle increase in time taken by the subjects to finish the test. We found that with a p-value of 0.0001, it is statistically significant.

Parameters	Friedman TMT-A								
	<b>MEAN</b>	<b>Differences</b>	Difference	$\pm SD$	test				
		in the	in %						
		means							
On	25.00			5.190	36.286	$0.0001*$			
discharge									
After 1	25.42	0.42	1.7%	5.914					
month									
After 3	25.55	0.55	2.2%	6.241					
month									
	*: Statistically significant								

**Table 3** – **Trail Making Test -A (TMT-A):**

**Graphical Representation 3: Trail Making Test -A (TMT-A):**



#### **2. Trail Making Test -B(TMT-B):**

In this Trail making test-B(TMT-B), we observed that the average time taken on discharge is 57.16 seconds, after one month is 57.54 seconds and after three months is 57.66 seconds. The difference in means from the day of discharge to after one month and after three months is 0.38 seconds and 0.5 seconds, respectively, which suggests that there is a subtle increase in time taken by the subjects to finish the test. We found that with a p-value of 0.0001, it is statistically significant.

**Table 4** – **Trail Making Test -B (TMT-B):**

Parameters		TMT-B	Friedman	P value					
	<b>MEAN</b>	<b>Differences</b>	Difference	$\pm SD$	test				
		in the	in $%$						
		means							
On	57.16			12.848	42.000	$0.0001*$			
discharge									
After 1	57.54	0.38	0.66%	13.576					
month									
After 3		0.5	0.87%						
month	57.66			13.836					
	*: Statistically significant								

## **Graphical Representation 4: Trail Making Test -B (TMT-B):**



## **3. PGI MEMORY SCALE:**

In this PGI Memory Scale, the average total score on discharge is 66.98. After one month is 65.77, and after three months is 64.60, which shows a decrease in the scores, and the differences in the means from the day of discharge to the after 1 month and three months are 1.21 and 2.38, respectively. We found that with a p-value of 0.0001, it is statistically significant.



#### **Table 5- PGI MEMORY SCALE**

# **Graphical Representation 5: PGI MEMORY SCALE**



#### **3.1 REMOTE MEMORY:**

This is the subtest of the PGI MEMORY SCALE. In this Remote memory, the subjective mean score on the day of discharge is 7.00. After 1 month, it is 6.90 and after 3 months is 6.78. The differences in the mean score after one month and after three months are 6.90 and 6.78, respectively. Even though the average mean scores are in the percentile range of 40 to 60 and the total score comes to 82-86, and the level of remote memory is good according to the PGI MEMORY scale, there is a subtle decrease in the levels which suggest of cognitive decline in the remote memory. We found that with a p-value of 0.0001, it is statistically significant.





## **Graphical Representation 6: REMOTE MEMORY**



### **3.2 RECENT MEMORY:**

This is the subtest of the PGI MEMORY SCALE. In this Recent memory, the subjective mean score on the day of discharge is 5.00. After 1 month, it is 4.90 and after 3 months is 4.77. The differences in the mean score after one month and after three months are 0.10 and 0.23, respectively. The average mean score is 5.00, which comes in the percentile range of 40 to 60, and the total score comes to 82-86, and level of recent memory is good according to the PGI MEMORY scale, but there is a subtle decrease in the levels .which suggest of cognitive decline in the recent memory. We found that with a p-value of 0.0001, it is statistically significant.

#### **Table 7- RECENT MEMORY:**



# **Graphical Representation 7: RECENT MEMORY:**



# **3.3 MENTAL BALANCE:**

This is the subtest of the PGI MEMORY SCALE. In this Mental Balance, the subjective mean score on the day of discharge is 6.46. After one month, it is 6.34, and after 3 months, it is 6.22. The differences in the mean score after one month and after three months are 0.12 and 0.24, respectively. The average mean scores are in the percentile range of 0 to 20 and 20 to 40, and the total score comes from 0 to 75 and 76 to 81, and the level of Mental balance is low to very low according to the PGI MEMORY scale. There is a subtle decrease in the levels, suggesting a cognitive decline in the Mental balance. We found that with a p-value of 0.0001, it is statistically significant.



# **Table 8- MENTAL BALANCE**

\*:Statistically significant

#### **Graphical Representation 8- MENTAL BALANCE**



#### **3.4 ATTENTION AND CONCENTRATION:**

This is the subtest of the PGI MEMORY SCALE. In this Attention and concentration, the subjective mean score on the day of discharge is 7.91. After 1 month, it is 7.75 and after 3 months is 6.78. The differences in the mean score after one month and after three months are 0.16 and 0.29, respectively. The average mean scores are in the percentile range of 0 to 20, and the total score comes from 0 to 75 and level of Attention and concentration is very low according to the PGI MEMORY scale, and there is a subtle decrease in the levels which suggest of cognitive decline in the Attention and concentration. We found that with a p-value of 0.0001, it is statistically significant.

Parameters		ATTENTION AND CONCENTRATION	Friedman	P value						
	<b>MEAN</b> <b>Differences</b>		Difference	$\pm SD$	test					
		in the	in $%$							
		means								
On discharge	7.91			1.320	42.000	$0.0001*$				
After 1 month	7.75	0.16	2.02%	1.601						
After 3 month	7.62	0.29	3.67%	1.905						
	*: Statistically significant									

**Table 9- ATTENTION AND CONCENTRATION**

## **Graphical Representation 9- ATTENTION AND CONCENTRATION:**



## **3.5 DELAYED RECALL:**

This is the subtest of the PGI MEMORY SCALE. In this Delayed recall, the subjective mean score on the day of discharge is 7.60. After one month, it is 7.44, and after 3 months, it is 7.32. The differences in the mean score after one month and after three months are 0.16 and 0.28, respectively. The average mean scores are in the percentile range of 20 to 40 and 0 to 20, and the total score comes to 76 to 81 and 0 to 75 level of Attention and concentration is low on the day of discharge, and the levels decreased to very low in the follow-ups according to the PGI MEMORY scale, which suggests of cognitive decline in the Delayed recall. We found that with a p-value of 0.0001, it is statistically significant.

## **Table 10. DELAYED RECALL**



## **Graphical Representation 10- DELAYED RECALL:**



50

# **3.6 IMMEDIATE RECALL:**

This is the subtest of the PGI MEMORY SCALE. In this Immediate Recall, the subjective mean score on the day of discharge is 5.57. After 1 month, it is 5.45 and after 3 months is 5.33. The differences in the mean score after one month and after three months are 0.12 and 0.24, respectively. The average mean scores are in the percentile range of 0 to 20. The total score comes from 0 to 75, and the level of Immediate recall is very low according to the PGI MEMORY scale. There is a subtle decrease in the levels, which suggest of cognitive decline in Immediate recall. We found that with a p-value of 0.0001, it is statistically significant.



#### **Table 11- IMMEDIATE RECALL**



#### **3.7 VERBAL RETENTION FOR SIMILAR PAIRS:**

This is the subtest of the PGI MEMORY SCALE. In this Verbal retention for similar pairs, the subjective mean score on the day of discharge is 5.00. After one month, it is 4.90, and after 3 months, it is 4.78. The differences in the mean score after one month and after three months are 0.1 and 0.22, respectively. The average mean scores are in the percentile range of 40 to 60, and the total score comes to 82 to 86, and the level of Verbal retention for similar pairs is good according to the PGI MEMORY scale. There is a subtle decrease in the levels, which suggest of cognitive decline in Verbal retention for similar pairs. We found that with a p-value of 0.0001, it is statistically significant.

Parameters		<b>VERBAL RETENTION FOR SIMILAR</b>	Friedman	P value				
		<b>PAIRS</b>	test					
	<b>MEAN</b>	<b>Differences</b>	<b>Difference</b>					
		in the						
		means						
On discharge	5.00			0.00	42.000	$0.0001*$		
After 1 month	4.90	0.1	2%	0.30				
After 3 month	4.78	0.22						
*: Statistically significant								

**Table 12- VERBAL RETENTION FOR SIMILAR PAIRS**

## **Graphical Representation 12- VERBAL RETENTION FOR SIMILAR PAIRS:**



### **3.8 VERBAL RETENTION FOR DISSIMILAR PAIRS:**

This is the subtest of the PGI MEMORY SCALE. In this Verbal retention for Dissimilar pairs, the subjective mean score on the day of discharge is 10.14. After one month, it is 9.99 and after 3 months is 9.81. The differences in the mean score after one month and after three months are 0.15 and 0.33, respectively. The average mean scores are in the percentile range of 20 to 40, the total score comes to 76 to 81, and the level of Verbal retention for Dissimilar pairs is Low according to the PGI MEMORY scale. There is a subtle decrease in the levels, which suggest of cognitive decline in Verbal retention for dissimilar pairs. We found that with a pvalue of 0.0001, it is statistically significant.

<b>Parameters</b>		<b>VERBAL RETENTION FOR DISSIMILAR</b>	Friedman	P value				
		<b>PAIRS</b>	test					
	<b>MEA</b>	<b>Differences</b>						
	N	in the						
		means						
On discharge	10.14			1.23	40.095	$0.0001*$		
After 1 month	9.99	0.15	1.47%	1.50				
After 3 month	9.81	0.33						
*: Statistically significant								

**Table 13 VERBAL RETENTION FOR DISSIMILAR PAIRS:**





## **3.9 VISUAL RETENTION:**

This is the subtest of the PGI MEMORY SCALE. In this Visual retention, the subjective mean score on the day of discharge is 4.91. After 1 month is 4.81 and after 3 months is 4.8. The differences in the mean score after one month and after three months are 0.1 and 0.11, respectively. The average mean scores are in the percentile range of 20 to 40, the total score comes to 76 to 81, and the level of Verbal retention for Dissimilar pairs is Low according to the PGI MEMORY scale. There is a subtle decrease in the levels, which suggest of cognitive decline in Verbal retention for dissimilar pairs. We found that with a p-value of 0.0001, it is statistically significant.

#### **Table 14- VISUAL RETENTION:**



## **Graphical Representation 14- VISUAL RETENTION:**



## **3.10 VISUAL RECOGNITION:**

This is the subtest of the PGI MEMORY SCALE. In this Visual recognition, the subjective mean score on the day of discharge is 7.39. After one month, it is 7.29, and after 3 months, it is 7.17. The differences in the mean score after one month and after three months are 0.1 and 0.22, respectively. The average mean scores are in the percentile range of 0 to 20, the total score comes from 0 to 75, and the level of Visual recognition is very low according to the PGI MEMORY scale. There is a subtle decrease in the levels, which suggests a cognitive decline in Visual recognition. We found that with a p-value of 0.0001, it is statistically significant.



#### **Table 15 VISUAL RECOGNITION**

# **Graphical Representation 15- VISUAL RECOGNITION:**



## **4.0 MAZE TEST 1:**

In this Maze Test 1, we observed that the average time taken to complete the test on discharge is 11.80 seconds. After one month is 12.11 seconds, and after three months is 12.23 seconds. The difference in means from the day of discharge to after one month and after three months is 0.31 seconds and 0.43 seconds, respectively. This suggests that there is a subtle increase in time taken by the subjects to finish the test. We found that with a p-value of 0.0001, it is statistically significant

# **Table 16- MAZE TEST 1:**



# **Graphical Representation 16: MAZE TEST 1:**



## **4.1 MAZE TEST 2:**

In this Maze Test 2, we observed that the average time taken to complete the test on discharge is 15.11 seconds. After one month is 15.57 seconds, and after three months is 15.69 seconds. The difference in means from the day of discharge to after one month and after three months is 0.46 seconds and 0.58 seconds, respectively. Which suggests that there is a subtle increase in the time taken by the subjects to complete the test. We found that with a p-value of 0.0001, it is statistically significant

# **Table 17- MAZE TEST 2:**



## **Graphical Representation 17- MAZE TEST 2:**



# **4.2 DIGIT SYMBOL SUBSTITUITON TEST(DSST):**

In this DSST, we observed that the average score on discharge is 84.61, after one month is 84.18 and after three months is 84.03. The difference in means from the day of discharge to after one month and after three months is 0.43 and 0.58, respectively, which suggests that there is a subtle decrease in time taken by the subjects to finish the test. We found that with a p-value of 0.0001, it is statistically significant.

**Table 18- DIGIT SYMBOL SUBSTITUITON TEST(DSST):**

Parameters		<b>DSST</b>	Friedman	P value				
	<b>MEAN</b>	<b>Differences</b>	Difference	$\pm SD$	test			
	in $%$ in the							
		means						
On discharge	84.61			3.092	43.000	$0.0001*$		
After 1 month	84.18	0.43	0.51%	3.494				
After 3 month	84.03	0.58	0.68%	3.708				
*: Statistically significant								

## **Graphical Representation 18- DIGIT SYMBOL SUBSTITUITON TEST(DSST):**



# **4.3 MINI-MENTAL STATE EXAMINATION (MMSE):**

In this MMSE, we observed that the average score on discharge is 25.57, after one month is 25.17 and after three months is 25.04. The difference in means from the day of discharge to after one month and after three months is 0.4 and 0.53, respectively, which suggests that there is a subtle decrease in the score. We found that with a p-value of 0.0001, it is statistically significant.

		<b>MMSE</b>	Friedman	P value				
Parameters	<b>MEAN</b>	<b>Differences</b>	<b>Difference</b>	$\pm SD$	test			
		in the	in $%$					
		means						
On discharge	25.57			2.410	42.000	$0.0001*$		
After 1 month	25.17	0.4	1.56%	3.251				
After 3 month	25.04	0.53	2.07%	3.566				
*: Statistically significant								

**Table 19- MINI-MENTAL STATE EXAMINATION (MMSE):**

# **Graphical presentation- 19- MINI-MENTAL STATE EXAMINATION (MMSE):**



**Table 20- Summary table**

	On discharge		After 1 month		After 3 month		Friedma	P value
<b>PARAMETERS</b>	<b>MEAN</b>	$\pm SD$	<b>MEAN</b>	$\pm SD$	<b>MEAN</b>	$\pm SD$	n test	
TMT A	25.00	5.190	25.42	5.914	25.55	6.241	36.286	$0.0001*$
TMT B	57.16	12.848	57.54	13.576	57.66	13.836	42.000	$0.0001*$
<b>PGI MEMORY</b>	66.98	6.421	65.77	9.208	64.60	12.308	43.517	$0.0001*$
<b>REMOTE</b> <b>MEMORY</b>	7.00	0.000	6.90	0.304	6.78	0.678	42.000	$0.0001*$
<b>RECENT MEMORY</b>	5.00	0.000	4.90	0.304	4.77	0.680	43.000	$0.0001*$
<b>MENTAL</b> <b>BALANCE</b>	6.46	0.668	6.34	0.929	6.22	1.259	42.000	$0.0001*$
<b>ATTENTION AND</b> <b>CONCENTRATION</b>	7.91	1.320	7.75	1.601	7.62	1.905	42.000	0.0001
<b>DELAYED RECALL</b>	7.60	1.096	7.44	1.415	7.32	1.730	42.000	$0.0001*$
<b>IMMEDIATE</b> <b>RECALL</b>	5.57	1.025	5.45	1.186	5.33	1.468	36.940	$0.0001*$
<b>VERBAL</b> <b>RETENTION FOR</b> <b>SIMILAR PAIRS</b>	5.00	0.000	4.90	0.304	4.78	0.678	42.000	$0.0001*$
<b>VERBAL</b> <b>RETENTION FOR</b> <b>DISSIMILAR PAIRS</b>	10.14	1.235	9.99	1.500	9.81	1.604	40.095	$0.0001*$
<b>VISUAL</b> <b>RETENTION</b>	4.91	1.349	4.81	1.574	4.8	1.585	40.925	$0.0001*$
<b>VISUAL</b> <b>RECOGNITION</b>	7.39	1.384	7.29	1.572	7.17	1.858	41.518	$0.0001*$
<b>MAZE TEST 1</b>	11.80	2.411	12.11	3.206	12.23	3.550	42.000	$0.0001*$
<b>MAZE TEST 2</b>	15.11	3.495	15.57	4.244	15.69	4.541	40.000	$0.0001*$
<b>DSST</b>	84.61	3.092	84.18	3.494	84.03	3.708	43.000	$0.0001*$
<b>MMSE</b>	25.57	2.410	25.17	3.251	25.04	3.566	42.000	$0.0001*$

#### **DISCUSSION:**

Out of 205 patients enrolled In the study, 75 patients belonged to the age group of 40 to 49 years, followed by 67 patients in 50 to 60 years, 47 patients in the age group of 30 to 39 years,15 patients in 20 to 29 years, whereas only one patient was below 20 years, the mean age being  $44.10 \pm 9.64$  years.

In Hampshire et al., a study from Germany, they did studies on large sample of 86,285 and the mean age group was  $46.75 \pm 15.73$  years<sup>174</sup>.

In a study done by Shwetha Jakhmola et al.,in the year 2021, the age group of 20 to 49 years was more exposed to the virus in India.

In a study done by Hetong Zhou et al., in the year 2020 the mean age was  $47\pm 10.54$  years, which is almost similar to the results of our study<sup>159</sup>.

In the study by Flavia Mattioli et al.,in the year 2021 the mean age was 47.76 years, the results of which are in accordance with the results of our study<sup>160</sup>.

In contradiction to our study, the mean age was  $74.5\pm3.8$  years in a study done by Tiina Savikangas et al. ina year 2021<sup>161</sup>.

In a other study by Jinghuan Gan et al.,in the year 2021, to study the impact of the COVID-19 pandemic on Alzheimer's disease and other dementias, the mean age was 70.62±7.96 years, the mean age was more than our study because they included the patients of Alzheimer's and other dementias and moreover in our study under exclusion criteria the age cut-off was 18 years to 60 years<sup>162</sup>.

# **Gender distribution:**

In our study, there was a male preponderance, with 147 males and 58 females ,probably because of more activity of males outdoors.

In a study done by Shwetha Jakhmola et al.,in the year 2021, the males were more exposed when compared to females because many of them serve in the society compared to the other age groups ,who stayed at home.Moreover,the COVID-19 mortatlity analysis revealed a major population from India is in the age group 20 to 49 years compared to the other countries.Availability of adequate health facilities,access to health resources and detection of infection in developing countries than in the developed countries can be contributing factors . In the study done by Hetong Zhou et al., 62 % of the patients were males, while 38% Were females, which also had male preponderance<sup>159</sup>.

In contrary to the results of our study, 75% of the patients were females in study by Flavia Mattioli<sup>160</sup>.

#### **Psychological assessments:**

#### **TMT :**

It was observed in our study that the average time taken to complete TMT-A at the time of discharge was 25 seconds where as an average time of 25.2 seconds was taken by the patients after one month of discharge, while the mean time taken was 25.55 after the three months of discharge. These results indicate that the time taken by the subjects to complete the test was increased after one month and three months, compared to the time of discharge, suggesting that there was a significant cognitive impairment, affecting the visual scanning and visuomotor tracking, thus affecting the speed of processing among COVID-19 recovered patients after a period of three months  $(p<0.05)$ .

On evaluation with TMT-B,57.16 seconds was the average time taken to complete the test at the time of discharge, while the patients took 57.54 seconds on average after one month and 57.66 seconds after three months. It was found that there was a subtle increase in time taken by the subjects to complete the test at three months when compared to that at the time of discharge, and the association between the average time taken and the time period of evaluation was statistically significant. (p<0.001).

In a study done by Becker et al., in the year 2021 where he they used TMT A and B as one of the assessment methods and found that there was relatively higher rates of impairment in cognition were present after several months of COVID-19 recovery .Acccording to their study defecits were present in executive functions and processing speed which were in accordance with our study<sup>163</sup>

Hetong zhou et al., in their study, found that the average time taken to complete the TMT was  $47.82 \pm 16.55$  seconds which was in accordance with our study<sup>159</sup>.

In a study done by Adouni et al ., they found that the minimum and maximum time taken by the subjects to complete the TMT-A was 20 seconds and 309 seconds respectively where as the minimum and maximum time taken by the subjects to complete the TMT-B was 41 and 340 seconds respectively<sup>164</sup>.

The results of our study indicate that the information processing speed of the subjects decreases following recovery from COVID-19 infection.

TMT is used commonly as a measure of Frontal Lobe functions like Executive functions which include Planning,Organising ,Sequencing and Multitasking.It is also a measure of behaviuoral difficulties like Agression ,Apathy and Disinhibition .

Therefore ,with the results we conclude that there is subtle decrease in the cognitive functions of Frontal Lobe in Executive functions.

#### **PGI MEMORY SCALE(PGIMS):**

To our knowledge, ours was the first study to determine cognitive impairment among COVID-19 recovered patients with the help of PGI MEMORY SCALE.

Remote memory, the subtest of the PGI MEMORY scale, was observed to decrease among COVID-19 recovered patients after three months of discharge when compared to the time of discharge. Although the mean scores were in the percentile range of 40 to 60, the level of remote memory being good according to the PGI MEMORY SCALE, the variations of mean scores within the percentile range was suggestive of cognitive decline in remote memory after three months of discharge which was statistically significant.

While the mean scores after one month and after three months differed from the time of discharge by 0.10 and 0.23, respectively, in the recent memory subset of PGI MEMORY SCALE, the scores were in the range of 40 to 60, indicating a good level of recent memory according to PGI MEMORY SCALE despite being under the common percentile range there was a subtle decline in the cognitive function in recent memory which was statistically significant(p=0.001).

There was also a decline of average scores in the Mental balance subset of PGI MEMORY SCALE from 6.46 on the day of discharge to 6.34 at one month and 6.22 after three months of discharge. There was a decrease in cognitive function in the mental balance subset, with the average scores falling under low to very low levels of mental balance, according to PGI MEMORY SCALE. There was a statistically significant association between the level of mental balance and the time of evaluation with the PGI memory scale

In a study done by Becker et al., in the year 2021 along with the TMT A and B they also used assessments like Phonemic and Category fluency which test language , similarly in our study the assessment Mental balance does the same.According to their study, defecits were present in the Category fluency which is in accordance to our study<sup>163</sup>.

Attention and concentration, the subtest of the PGI MEMORY scale, was observed to decrease among COVID-19 recovered patients after three months of discharge when compared to the time of discharge. Although the mean scores were in the percentile range of 0 to 20, the level of Attention and concentration being very low according to the PGI MEMORY SCALE, the variations of mean scores within the percentile range were suggestive of cognitive decline in Attention and concentration after three months of discharge which was statistically significant.  $(P=0.001)$ .

In another subtest of the PGI MEMORY scale, the Delayed recall, the mean score on the day of discharge was 7.60,7.44 after one month and 7.32 after three months, the scores in the percentile range of 20 to 40 and 0 to 20, the level of delayed recall being low on the day of discharge and the levels decreased to very low after three months according to the PGI MEMORY scale.

In a study done by Becker et al., in the year 2021 they also used assessments for Memory encoding and recall and they found that there were defecits in these areas<sup>163</sup>.

The immediate recall subtest of the PGI memory scale showed a decline in the levels of cognitive function at three months after discharge compared to the time of discharge. The average mean score is 5.57 at discharge,5.45 after one month and 5.33 after three months. The mean scores lie in the percentile range of 0 to 20, rendering a very low level of immediate

recall, which was statistically significant (p=0.001).

While the mean scores after one month and after three months differed from the time of discharge by 0.1 and 0.22, respectively, in the verbal retention for similar pairs subtest of PGI MEMORY SCALE, the scores were in the range of 40 to 60, indicating a good level of verbal retention for similar pairs according to PGI MEMORY SCALE despite being under the common percentile range there was a subtle decline in the cognitive function in verbal retention for similar pairs which was statistically significant( $p=0.001$ ).

With a subjective mean score of 10.14 on the day of discharge, 9.99 after one month and 9.81 after three months, the mean scores fell under the percentile range of 20 to 40, indicating a low level of verbal retention of dissimilar pairs according to PGI memory scale, also suggesting a cognitive decline after three months of discharge which was statistically significant.

Visual retention, the subtest of the PGI MEMORY scale, was observed to decrease among COVID-19 recovered patients after three months of discharge when compared to the time of discharge. Although the mean scores were in the percentile range of 0 to 20, the level of Visual retention is very low according to the PGI MEMORY SCALE. The variations of mean scores within the percentile range were suggestive of cognitive decline in Attention and concentration after three months of discharge which was statistically significant. (P=0.001).

65

In another subtest of the PGI memory scale, the visual recognition, the subjective mean score on the day of discharge was 7.39. After one month was 7.29 and after 3 months, is 7.17, the average score being in the percentile range of 0 to 20, indicating a very low level of visual recognition according to the PGI memory scale. There was a decline in the cognitive function among the COVID-19 recovered patients after three months of discharge which was statistically significant.

In a study done by Davis et al., in 2021 by using assessment methods like Qualtrics which contains 257 questions ,they also used MRI brain if memory or cognitive dysfunctions were present and foud that 88.0% of the study population showed Cognitive dysfunction and/or Memory loss <sup>165</sup>.

In a study done by Junyoung Oh et al., in the year 2022,they found that SARS-COV-2 spike proteins can induce cognitive defecits and even causes anxiety like symptoms in the mouse by causing Hippocampal neuronal deaths which causes memory defecits as hippocampus is responsible for memory<sup>166</sup>.

It is a comprehensive scale to measure Verbal and Non verbal memory which are the functions of Temporal Lobe.In our study we found that there was subtle decrease in the cognition in the domains of verbal and non verbal memory which suggest of Temporal lobe dysfunction.

#### **MAZE TEST 1:**

The average time taken to complete the maze test 1 was increased by 0.43 seconds at three months after discharge when compared to the day of discharge, and a difference of 0.31 seconds was observed between the first month of discharge and the time of discharge.

These results indicated that there was a cognitive dysfunction in the Visual memory and was statistically significant.

66

#### **MAZE TEST 2:**

The average time taken to complete maze test 2 was 15.11 seconds during discharge, compared to 15.57 seconds after one month of discharge and 15.69 seconds after three months of discharge.

The increase in time taken to complete the test after a period of three months suggest a cognitive dysfunction in COVID-19 recovered patients, which was statistically significant.

The maze test is used to assess the executive functions of the frontal lobe like planning, multitasking, organising sequence and impulse control. The results of our study indicate that the functions of the frontal lobe have been affected after three months following COVID-19 infection.

In a study done by Adouni et al .,the minimum and maximum time taken by the subjects to complete the Maze test was 7 seconds and 139 seconds respectively and the mean was 59 seconds this is because the mean age in the study was  $63\pm12.7$  which suggest that higher the age group the time taken to complete the test was high and the chances of cognitive defecits were also high $164$ .

Maze test is also a measure of Frontal Lobe where the Executive functions and Behaviuor changes can be identified .

In our study we found that there was with the help of Maze Test 1 and 2, there was subtle decline in the cognition in the domains related to the Frontal Lobe.

#### **DSST:**

DSST score was calculated as the number of correctly matched symbols in 120 seconds. In our study, the mean score on discharge was 84.61, whereas the average score after one month after discharge was 84.18 and 84.03 at three months of discharge.

Similar to the other tests done to determine cognitive dysfunction, DSST also showed declining cognitive function, which was also statistically significant.

In a study done by clement Gouraud et al., the mean DSST score was 50, which was lesser than the results of our study. The contrasting results might be due to the inclusion of elderly patients in their study, where the mean age was 60 years as opposed to the mean age of  $44.10\pm9.64$ years in our study<sup>167</sup>.

DSST is a subtest of WAIS(Wechsler Adult Intelligence scale) to assess the psychomotor speed, sustained attention and logical reasoning and visuo perceptual the parameters that have been affected amongst the patients in our study following three months of COVID-19 infection. **MMSE:**

The average MMSE score was 25.57 at the time of discharge,25.17 after one month of discharge and 25.04 after three months of discharge. Although there was a subtle decline in the scores, the mean score of 25 suggests no cognitive impairment. This could be attributed to the fact that MMSE helps to detect severe cognitive dysfunctions as that seen in neurodegenerative diseases. Hence there is no cognitive impairment among the patients enrolled in our study.

In a study by clement Goudaurd et al., the mean MMSE score was 28, which was also suggestive of no cognitive impairment, the results of which are in accordance with our study<sup>167</sup>. In another study by Flavia Mattioli et al., where the neurological and cognitive sequelae of COVID-19 patients were studied on a four-month follow-up, there was no cognitive impairment based on the MMSE score among the patients<sup>160</sup>.

In another study by Jhinguan Gan et al., there was a severe cognitive impairment among the subjects enrolled, which is in contrast with the results in our study. The severe cognitive impairment could be attributed to the long-term follow-up of their patients compared to only three months of follow-up in our study<sup>162</sup>.

In a Systematic review and Meta analysis study that is Impact of COVID-19 on Cognitive Function done by Sarah Houben in the year 2022 concluded that after COVID-19 infection the individuals are more prone to the Cognitive decline.According to this Meta analysis,MoCA was the assessment which was used most and found that it could mild cognitive defecits and

68

moreover MoCA is available in more than 100 languages. where as the next study which was used more frequently after the MoCA was MMSE.Among the both assessments MoCA could detect the subclinical defecits and can clearly discriminated when compared with MMSE<sup>168</sup>.

In a study done by Woo et al., in the year 2020 by using Modified Telephone interview for cognitive status (TICS-M) found that subclinical sustatined cognitive decline may be a common complication in a COVID-19 recovered adults of younger age<sup>169</sup>.

Alemanno et al., in a study done in 2021 using assessment methods like MoCA(Montreal Cognitive Assessment) and MMSE,concluded that 80% of the subjects showed cognitive impairment and 40% showed mild to moderate Depression<sup>170</sup>.

In a study done by Amalakanti et al.,in 2021 using MoCA concluded that even asymptomatic COVID-19 patients had cognitive impairments which suggest that there is a requirement of detailed Neuropsychological assessment especially in a elderly population<sup>171</sup>.

In a study done by Del Brutto et al., in 2021 using MoCA found that there was cognitive decline in a patients of mild COVID-19 infection<sup>172</sup>.

In a study done by Dressing et al., in the year 2021 found that they could determine cognitive dysfunction after six months of COVID-19 infection ,neuronal causes could be the possible reason to the high prevalence of tiredness<sup>173</sup>.

Hampshire et al., in the year 2021 by using Great British intelligence Test found that COVID-19 patients exhibited cognitive defecits when compared to controls.They also found that people who had been hopsitalized were having higher degree of cognitive defecits <sup>174</sup>.

In a study by vyas et al., in the year 2021 used Brain Fog synptoms questionnaire and found that Brain fog can happen as a complication in COVID-19 survivors and it occurs in higher rates in patients who required oxygen and who were on Ventilator 175 .

69

# **LIMITATIONS:**

- ➢ In this study we have evaluated the immediate effects of SARS-CoV-2 infection on cognitive function , since the certain neuropsychological assessments were done only for a short period after the COVID-19 patients recovered.
- $\triangleright$  In this study we didn't use control group.
- $\triangleright$  In this study we didn't assess psychopathology.
- $\triangleright$  In this study we didn't correlate with the Neuroimaging
- ➢ Finally, we did not assess the influence of antiviral therapy and steroidal therapy on cognitive functions.

## **Conclusion:**

In this study, most of the patients belong to the age group of 40 to 49 years, with male predominance. Several neuropsychological tests have been administered to determine the cognitive functions of recovered COVID-19 patients over a period of three months.

The average scores of TMT A and B, all the subtests of the PGI memory scale, Maze tests 1 and 2, and DSST showed a subtle decline in cognitive function after three months of recovery from COVID-19.

However, according to the MMSE score, there was no cognitive impairment among the patients, which could be due to the ability of MMSE to identify severe cognitive impairment when compared to other tests that could determine even a slight decrease in cognitive function.

Our study provided helpful insight into the effect of COVID-19 on neuropsychological manifestations in the affected patients. These findings also indicate that there will be an influx of patients in the near future with more cognitive dysfunctions. Hence any cognitive complaints after the episode of COVID-19 should be considered significant, and a long-term follow-up is necessary to identify the progress of the cognitive status, which could help in early intervention and prompt treatment.

In our study, though there was a cognitive decline, whether this cognitive dysfunction is transient or would progress was not established. Hence studies of larger magnitude and longer duration are required to assess the cognitive status of a COVID-19 recovered individual.

#### **SUMMARY**

- 1. Out of 205 patients enrolled In the study, 75 patients belonged to the age group of 40 to 49 years, followed by 67 patients in 50 to 60 years, 47 patients in the age group of 30 to 39 years,15 patients in 20 to 29 years, whereas only one patient was below 20 years, the mean age being  $44.10 \pm 9.64$  years.
- 2. In our study, there was a male preponderance, with 147 males and 58 females ,probably because of more activity of males outdoors.
- 3. The males were more exposed when compared to females because many of them serve in the society compared to the other age groups ,who stayed at home.
- 4. TMT is used commonly as a measure of Frontal Lobe functions like Executive functions which include Planning, Organising ,Sequencing and Multitasking. Therefore,with the results we conclude that there is subtle decrease in the cognitive decline in the functions of Frontal Lobe in Executive functions.
- 5. To our knowledge, ours was the first study to determine cognitive impairment among COVID-19 recovered patients with the help of PGI MEMORY SCALE.
- 6. Remote memory, the subtest of the PGIMS, the variations of mean scores within the percentile range was suggestive of cognitive decline in remote memory after three months of discharge which was statistically significant.
- 7. While the mean scores after one month and after three months differed from the time of discharge , in the recent memory subset of PGIMS, indicating a good level of recent memory according to PGI MEMORY SCALE despite being under the common percentile range there was a subtle decline in the cognitive function in recent memory which was statistically significant( $p=0.001$ ).
- 8. There was a decrease in cognitive function in the mental balance subset, with the average scores falling under low to very low levels of mental balance, according to PGI MEMORY

SCALE. There was a statistically significant association between the level of mental balance and the time of evaluation with the PGI memory scale.

- 9. Attention and concentration, the subtest of the PGI MEMORY scale, was observed to decrease among COVID-19 recovered patients after three months of discharge when compared to the time of discharge.
- 10. In another subtest of the PGI MEMORY scale, the Delayed recall, the levels decreased to very low after three months according to the PGI MEMORY scale.
- 11. The immediate recall subtest of the PGI memory scale showed a decline in the levels of cognitive function at three months after discharge compared to the time of discharge.
- 12. In the verbal retention for similar pairs subtest of PGI MEMORY SCALE, indicating a good level of verbal retention for similar pairs according to PGI MEMORY SCALE despite being under the common percentile range there was a subtle decline in the cognitive function in verbal retention for similar pairs which was statistically significant( $p=0.001$ ).
- 13. Indicating a low level of verbal retention of dissimilar pairs according to PGI memory scale, also suggesting a cognitive decline after three months of discharge which was statistically significant.
- 14. Visual retention, the subtest of the PGI MEMORY scale, was observed to decrease among COVID-19 recovered patients after three months of discharge when compared to the time of discharge.
- 15. In another subtest of the PGI memory scale, the visual recognition, indicating a very low level of visual recognition according to the PGI memory scale. There was a decline in the cognitive function among the COVID-19 recovered patients after three months of discharge which was statistically significant.
- 16. PGIMS is a comprehensive scale to measure Verbal and Non-verbal memory which are the functions of Temporal Lobe. In our study we found that there was subtle decrease in the

cognition in the domains of verbal and non-verbal memory which suggest of Temporal lobe dysfunction.

- 17. The average time taken to complete the maze test 1 was increased these results indicated that there was a cognitive dysfunction in the Visual memory and was statistically significant.
- 18. The average time taken to complete maze test 2 was increased after a period of three months suggest a cognitive dysfunction in COVID-19 recovered patients, which was statistically significant.
- 19. The maze test is used to assess the executive functions of the frontal lobe like planning, multitasking, organising sequence and impulse control. The results of our study indicate that the functions of the frontal lobe have been affected after three months following COVID-19 infection.
- 20. Maze test is also a measure of Frontal Lobe where the Executive functions and Behaviour changes can be identified .
- 21. In our study we found that there was with the help of Maze Test 1 and 2 ,there was subtle decline in the cognition in the domains related to the Frontal Lobe.
- 22. Similar to the other tests done to determine cognitive dysfunction, DSST also showed declining cognitive function, which was also statistically significant.
- 23. DSST is a subtest of WAIS(Wechsler Adult Intelligence scale) to assess the psychomotor speed, sustained attention and logical reasoning and visuo perceptual the parameters that have been affected amongst the patients in our study following three months of COVID-19 infection.
- 24. Although there was a subtle decline in the scores of MMSE, the mean score of 25 suggests no cognitive impairment. This could be attributed to the fact that MMSE helps to detect severe cognitive dysfunctions as that seen in neurodegenerative diseases. Hence there is no cognitive impairment among the patients enrolled in our study according to the MMSE.

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B.L.D.E. (DEEMED TO BE UNIVERSITY) (Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGO Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

## **INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE**

The Institutional ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Assessment of Cognitive function in COVID-19 Recovered patients.

Name of PG student: Dr M.Bhargava Swaraj, Department of Psychiatry

Name of Guide/Co-investigator: Dr Santosh Ramdurg, Associate Professor of Psychiatry

DR

CHAIRMAN, IEC Institutional Ethical Committee **BLDE** (Deemed to be University) Shri E.M. Press Medical College, VIJAYAPUR-500103 (Karnataka)

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Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project

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- 2. Copy of informed consent form
- 3. Any other relevant documents.

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#### B.L.D.E. (DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH

#### CENTER, VIJAYAPURA-586103

#### INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned, The undersigned,  $S/O D/O W/O$  , aged years, ordinarily resident of \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ do hereby state/declare that Dr. MEKALA BHARGAVA SWARAJ of Shri. B. M. Patil Medical College Hospital and Research Centre has explained me thoroughly on \_at vijayapura(place) and it has been explained to me in my own language that I am recovering from COVID19 disease (condition). Further Doctor Dr. MEKALA BHARGAVA SWARAJ informed me that he is conducting dissertation/research titled "ASSESSMENT OF COGNITIVE FUNCTIONS IN COVID-19 RECOVERED PATIENTS" under the guidance of Dr. SANTOSH RAMDURG requesting my participation in the study. Apart from routine treatment procedure, followup observations will be utilized for the study as reference data. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of other similar cases in near future.

The Doctor has also informed me that information given by me, observations made photographs, video graphs taken upon me by the investigator will be kept confidential and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis.

At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.



## **BLDE'S SHRI B.M. PATIL MEDICAL COLLEGE**

## **HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR.**

# ―**ASSESSMENT OF COGNITIVE FUNCTION IN COVID-19 RECOVERED PATIENTS**"



Residence:

Address and Mobile number:

Method of diagnosing of covid-19: chest x-ray/Rapid Antigen Antibody test/

RT-PCR/HRCT

SEVERITY: MILD /MODERATE/SEVERE Previous history of Major medical illness:

- HYPERTENSION:
- DIABETES MELLITUS:
- COPD:
- ANY OPTHER SPECIFY

Previous history of:

- Head injury:
- Mental Retardation:
- Cognitive decline:

Previous history of Mental illness:

Vitals at the time of Admission: PR:

BP: RR: Temp:

Oxygen saturation on the day of

Admission:

Vitals at the time of Discharge: PR:

BP: RR: Temp:



### SR.NO IP NO/ PATIENT ID PHONE NUMBESF ID NO

AGE SEX

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**MMSE** 

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