

Review article

# Immunity and Mental Health: Towards COVID-19

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## ABSTRACT

**Introduction:** The Corona virus that originated in China in December 2019, has now spread rapidly globally. It is highly contagious & to date no cure in form of vaccine or medicines is available.

**COVID-19 and Immunity:** Enhancing body's natural defense system plays an important role in maintaining optimum health. The serum levels of IL2R and IL-6 in patients with COVID-19 are positively correlated with the severity of the disease. Studies have found that, compared with COVID-19 patients from general wards, patients in the intensive care unit [ICU] display increased serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF- $\alpha$ .

**COVID-19 and Mental Health:** Patients who had positive COVID-19 diagnosis reported significantly elevated levels of corona virus anxiety compared to their non-infected, but anxious peers, this highlights the clinical utility of the Corona Anxiety Scores [CAS] & the importance of assessing, treating the psychological needs of those infected with the virus. The need to formulate psychological interventions to improve mental health and psychological resilience during COVID-19 pandemic is the need of the hour. We need to tackle and fight the stigma, fear & anxiety related to the virus that is greater than the disease itself. Governments have provided mental health services to their citizens by varied channel including hotline, online consultation & course and outpatient consultation, but have indicated that more attention should be paid to depression and anxiety. As India's cases increase, the importance of following the government laid precautions becomes all the more important.

**Key words:** COVID-19, Corona Virus, Immunity, Mental Health

## INTRODUCTION

The novel Corona virus (2019-nCoV, officially known as SARS-CoV-2 or COVID-19) was first reported in December 2019, as a cluster of acute respiratory illness in Wuhan, Hubei Province, China. The novel Corona virus (2019-nCoV, officially known as SARS-CoV-2

or COVID-19) was first reported in December 2019, as a cluster of acute respiratory illness in Wuhan, Hubei Province, China. Since then, it has been spreading rapidly to over 215 countries and has been declared a global pandemic by the World Health Organization (WHO) on 12<sup>th</sup> March 2020. China had noticed cluster of cases of atypical pneumonia caused

by a virus, later which was identified as Novel Corona Virus in December 2019 [abbreviated as COVID-19], which has spread rapidly globally [1]. It has been found that the virus is highly homologous [80%] to SARS-CoV, which had caused acute respiratory distress syndrome [ARDS] and high mortality during 2002–2003, that's why severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2, 2019-nCoV] name was given to this virus [2]. First stage includes infection with SARS COVID-19 and the development of flu-like symptoms. Sometimes it can progress in pneumonia and even acute respiratory distress syndrome [ARDS]. In the second stage patients develop pulmonary inflammation and coagulopathy. The development of various biomarkers like C-reactive protein [CRP], ferritin, IL-6, IL-1, and D-dimer has been seen during this stage, which is associated with the development of acute respiratory distress syndrome with poor prognosis [3,4]. The third stage is the fibrosis. It has been reported in more than 200 countries with over 13,150,645 confirmed cases of COVID-19, including 574,464 deaths by 15.07.2020, as reported to WHO [5].

**Corona and Immunity:** In the wake of the COVID-19 outbreak, entire mankind across the globe is suffering. Enhancing body's immunity plays an important role in maintaining optimum health. We all know that prevention is better than cure. High virus titre and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality observed during the pathogenic Human Corona Virus [HCoV] infection. The experience from treating SARS and MERS shows that reducing viral load through interventions in the early stages of the disease and controlling inflammatory

responses through immune modulators are effective measures to improve the prognosis of HCoV infection [6]. High levels of expression of IL-1B, IFN- $\gamma$ , IP-10, and monocyte chemo attractant protein 1 [MCP-1] have been detected in patients with COVID-19. These inflammatory cytokines may activate the T helper type 1 [Th1] cell response [7]. Th1 activation is a key event in the activation of specific immunity [8]. However, unlike SARS patients, patients with COVID-19 also have elevated levels of Th2 cell secreted cytokines [such as IL-4 and IL-10], which inhibit the inflammatory response. The serum levels of IL2R and IL-6 in patients with COVID-19 are positively correlated with the severity of the disease [9]. Many studies have found that, compared with COVID-19 patients from general wards, patients in the intensive care unit [ICU] display increased serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF- $\alpha$ .

**Association of COVID-19 with Stress, Anxiety and Depression:** The outbreak of COVID-19 could also be stressful for people. Uncertainties related to prognosis, imposing strict unpleasant public health measures are diminishing personal freedom, job loss, financial loss, which lead to stressors that are causing emotional distress and putting the individual on increased risk of developing psychiatric illness. It may be indirectly related to COVID-19. It has been seen in the disaster mental health studies that emotional stress is inevitably present in the affected population. Immuno compromised individual person with co-morbidity like Chronic kidney disease, Coronary artery disease, Diabetes etc. and those with pre-existing psychiatric illness are particularly at high risk of mental stress.

Fear and anxiety are often overwhelming and cause strong emotions in adults and youngsters. Coping with stress will cause you to, the people you care about, and your community stronger. Stress during a communicable disease outbreak can include fear and worry about your own health and therefore the health of your loved ones, changes in sleep or eating pattern, difficulty in sleeping or concentrating, worsening of chronic health problems, worsening of mental health condition, increased use of alcohol, tobacco, or other drugs. People who may respond more strongly to the strain of a crisis include older people and other people with chronic diseases who are at higher risk for severe illness from COVID-19, children and teenagers, people that are helping with the response to COVID-19, like doctors, other health care providers. Changes to daily life have been swift and unprecedented, as cases of virus surge, the death toll escalates, and draconian measures to contain the spread of disease increase across the globe. Although there has been substantial attention to measures to identify people with the coronavirus infection yet identifying the mental health care needs of people impacted by this pandemic have been relatively neglected [10].

This is surprising given that mass tragedies, particularly ones that involve infectious diseases, often trigger waves of heightened fear and anxiety that are known to cause massive disruptions to the behavior and psychological well-being of many in the population [11]. For instance, during a recent, large survey of people highly susceptible to the corona virus infection [i.e. medical workers], the prevalence rate of traumatic stress was as

an alarming 73.4%, depression was at 50.7%, generalized anxiety was at 44.7%, and insomnia was at 36.1%. Although these findings are disturbing, they're not isolated, as research on the psychological impact of previous global disease outbreaks has demonstrated clear links between pandemic-related anxiety and elevated symptoms of stress, anxiety, contamination concerns, health anxiety, post-traumatic stress, and suicidality [12-16].

In fact, the finding that those with a positive COVID-19 diagnosis reported significantly elevated levels of coronavirus anxiety compared to their non-infected, but anxious peers, further highlight the clinical utility of the Corona Anxiety Scores [CAS] and the importance of assessing and treating the psychological needs of those infected with the virus [17]. If some expert opinions are correct, then that would mean that up to 70% of the world's population could potentially need both medical and psychological care with their COVID-19 infections [17, 18]. In China, during the initial phase of COVID-19 outbreak, half the respondents rated their psychological impact as moderate-to-severe, and about one-third reported moderate-to-severe anxiety. Female gender, student status, and specific physical symptoms were associated with a greater psychological impact of the outbreak and better levels of stress, anxiety, and depression. Specific up-to-date and accurate health information and certain precautionary measures were related with a lower psychological impact of the outbreak and lower levels of stress, anxiety, and depression [19]. Protecting health care workers is an important component of public health

measures for addressing COVID-19 epidemic. The findings of a study show that there is high prevalence of mental health problems, which positively associated with frequently social media exposure during the COVID-19 outbreak. These findings implicated the government need pay more attention to mental health among general population while combating COVID-19. Fortunately, the government has provided mental health services by varied channel including hotline, online consultation, online course and outpatient consultation, but more attention should be paid to depression and anxiety [20, 21]. In another survey, study of physicians and nurses in hospitals with fever clinics or wards for patients with COVID-19 in China, health care workers responding to the spread of COVID-19 reported high rates of symptoms of depression, anxiety, insomnia, and distress. Special interventions to maintain mental well-being of health care workers exposed to COVID-19 need to be immediately implemented, with women, nurses, and frontline workers requiring particular attention [22, 23]. During this pandemic, most of the educated people and health professionals are aware of this infection, possible preventive measures, the importance of social distancing and government initiatives taken to limit the spread of infection. However, there are increased worries and apprehensions among the general public regarding acquiring COVID-19 infection. People have higher perceived needs to deal with their mental health difficulties. There is a need to intensify the awareness program and address the mental health issues of people during this COVID-19 pandemic [24]. Online technologies could be harnessed to provide social support

networks and a sense of belonging [25], although there might be disparities in access to or literacy in digital resources. Interventions could simply involve more frequent telephone contact with close family and friends, voluntary organizations, or health-care professionals, or community outreach projects providing peer support throughout the enforced isolation. Beyond this, cognitive behavioral therapies could be delivered online to decrease loneliness and improve mental wellbeing [26]. It is important to study the mental health impacts in various populations [general populations, cases of COVID-19, and close contacts of COVID-19 and healthcare workers] for planning effective intervention strategies for them. A healthcare worker recently said "It is completely justified to be overwhelmed, but we know that panic and chaos can never side with you when you are managing a dying patient or a pandemic. There is lots to worry about amidst the increasing incidence, high transmissibility, non-conclusive treatment modalities, potential scarcity of personal protective equipment, crashing economy & unemployment that the world is facing, that you & I face". If we take at some point at a time, calmly that specialize in our role. Repeatedly like these, circumstances aren't in our control as in pandemic of corona virus but one are often on top of things of the inner environment where one can respond with calmness, courage, love and peace. The need to formulate psychological interventions to enhance psychological state and psychological resilience during COVID-19 epidemic is that the need of the hour. we'd like to tackle and fight the stigma, fear and anxiety associated with the

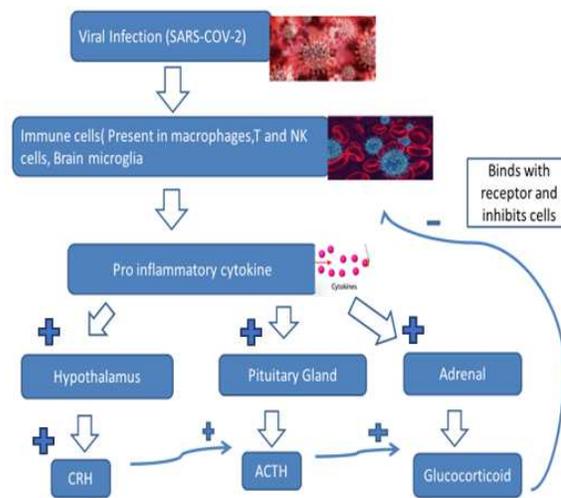
virus that's greater than disease itself.  
**Impact of social isolation on psychological state during COVID 19 pandemic**

One of the main steps is to avoid getting outside until emergency to stop community transmission and to attained the stagnant growth of the COVID 19[27]. However, this step is must but the social isolation goes to be an emerging explanation for negative impact on psychological state of society. Studies related during this regard showing, that quarantine during other epidemics like SARS and MERS had impacted negative psychological effects like Post traumatic stress disorder [PTSD], depression, anxiety and fear. Provoking factors for COVID impact on psychology are history of psychiatric illness, occupation associated with hospital or in high risk condition like police, airline workers, Housekeeping of economic building, frequent or longer quarantine duration, infection fears, boredom, insufficient supplies of protective equipment or insufficient supplies of primary requirements, insufficient information, and financial resources [28]. Recently an online survey has reported the outcome of COVID 19 pandemic on psychological impact and stress [20]. Out of 1210 subject 8.1% had moderate to severe stress, 28.8% had anxiety and 16.5% had depression symptoms. Peoples with inadequate knowledge or information had more probability for depression during epidemic, and people that suffered from the SARS-CoV-2 with mild symptoms like cough, running nose, sneezing, inflammation of mucous membrane, fever or history of chronic illness, also suffering significantly with anxiety, depression or stress. These findings suggest the need of adequate information related to COVID 19 spread in

simple language, and restrict the spread of rumors, and cooperation of media [29].

**Psycho- Neuroendocrine - Immune interaction in COVID 19**

It is hypothesized that Viral infection like SARS-CoV increases the hypothalamo-adrenal axis [HPA] activity via increasing proinflammatory cytokine release from immune cells like macrophages, T and NK cells or brain microglia. There is three main effects of cytokines on HPA.1. stimulating the corticotrophin releasing hormone secretion in the hypothalamus, 2. Stimulating the adreno-corticotropic hormone [ACTH] secretion in the pituitary, 3. Stimulating the glucocorticoid [cortisol] secretion from the adrenal cortex. All these three stimulating effects ultimately enhances the glucocorticoid release which combining with the receptor in the immune cells declines the proinflammatory cytokine release and synthesis [negative feedback] [Fig.1].



**Fig. 1: Mechanisms [Hypothetical] by which viral infection [SARS-CoV or COVID 19] may cause hyperactivity of the hypothalamus-pituitary-adrenal [HPA] as negative feedback to HPA and immune cells is dysfunctional**

As the similarity of COVID 19 with SARS-CoV, it is possible that it also causes the hyperactivity of HPA. Therefore, whenever there will be dysfunction of this negative feedback of HPA on immune system, decline of pro-inflammatory cytokine will not take place which eventually causes the cytokine storm and HPA hyperactivity [30].

Increase release level of cytokine or cytokine storm and dysfunction of glucocorticoid-immune axis may be the cause of infection related or stressors related increase hospital administration of cases of psychosis and schizophrenia. Hence future study is needed related to that, as infection of SARS or COVID may cause psychiatric illness [31].

### **Role of Cytokines and Mental Health**

Psychiatric disorders like depression, anxiety and psychosis also are known to be related to raised proinflammatory cytokines [32, 33]. There are evidences to point out the key role of cytokines in learning and memory. Increment in expression of genes of IL-1b, IL-1 receptor antagonist, IL-6 and IL-8 are reported in healthy individuals in hippocampus area of brain during future potentiation [LTP] of memories and learning within the different studies [34-36]. However, during peripheral and central diseases during which the brain levels of IL-1b and IL-6 are increased, both cytokines tend to inhibit the synaptic plasticity, learning, and memory [35]. Specifically, high levels of IL-6 were found in blood of SARS-CoV and SARS-CoV-2 infected patients, which may be liable for memory impairments in patients. Interleukin-6 is a known as a pleiotropic cytokine expressed in low levels in healthy individuals, within the presence of homeostasis alterations it

becomes higher and rapidly detected, and even after stress agent removal, its levels are often maintained elevated and cause diseases [37, 38]. Accordingly, a dysregulation of this cytokine expression counts for the event of psychiatric disorders [39]. The activation of the hypothalamic-pituitary-adrenocortical [HPA] axis has also been observed during pathologies involving an immune/inflammatory process, including viral infections [40]. It results in increment in glucocorticoid production, which may be a physiological response that contributes to avoid the deleterious effects of excessive production of inflammatory mediators and a non-specific recruitment of cells with no or low affinity for triggering antigens [41]. It seems reasonable to imagine a state hyperactivity of the HPA axis in infected patients, because of the "cytokine storm". A dysfunctional glucocorticoid-immune circuitry has been observed in schizophrenia. After a stress paradigm, while healthy patients experienced a rise in cortisol levels, negatively correlated to the next changes in IL-6 levels, patients with schizophrenia had elevated cortisol positively correlated to subsequent changes in IL-6 levels, suggesting an inability to down regulate the response of body in response to worry in psychiatric disorders [42]. Similarly, high levels of IL-6 are observed in patients of early psychosis [43]. Considering these findings together, it's possible that SARS CoV 19 infection, raised proinflammatory cytokines and therefore the development of psychiatric disorders could be interrelated [44]. Long-term effects of infection and inflammation have also been documented within the patients of previous sorts of SARS virus

survivors within the past [41]. Survivors of SARS, months or years after the acute phase of the infection, can also exhibit impaired memory, sleep disturbances, increased levels of stress, depression, anxiety, and PTSD symptoms [45-47]. This is associated by increased cytokine levels caused by the viral infection or social isolation or both. Increased cytokine levels lead to neuronal death, dysfunction in neurotransmitter release and in regulation of HPA axis. [30].

### **Preventive Measures and Precautions:**

We can move ahead with COVID-19, by taking some steps towards the life-style management

as precautions for psychological state disbalance like 1]. Think positively and encourage others by using social media, it'll strengthen the bond and mutual affection [48] 2]. Maintain good sleep hygiene and exercise compliance. 3]. Diet management [balanced diet] 4]. Avoid drug abuse, smoking, nutriment intake, excessive online activity or watching TV continuously, believing in fake news [49]. Policy for frontline healthcare workers and proper PPE supply consistent with demand are going to be an honest strategy to mitigate the impact of COVID on them. Regular breaks in between the work, or lesser working time, rotation in shift policy should be introduce for organization associated with high risk.[50]. Online consultation and awareness regarding the supply of psychological state professionals in emergency situation is another precaution for general population [48]. Neuroendocrine-immune responses triggered by stress, often decline with music and modulation of cytokine levels. Music therapy or art also decrease IL 6 levels. Therefore, music therapy and

art also are promising measures for improving psychological state [51]. Evidences are coming to support the link between changes within the body's immune reaction and neuro endocrine system to SARS CoV 2 infection. Maintenance of good immunity, consumption of nutrient diet, consumption of vitamins especially C and E with yoga and exercises help in fighting COVID-19 infection. Precautionary measures against COVID-19 variables included avoidance of sharing of utensils [e.g., chopsticks] during meals, covering mouth when coughing and sneezing, washing hands with soap, washing hands immediately after coughing, sneezing, or rubbing the nose, washing hands after touching contaminated objects, and wearing a mask regardless of the presence or absence of symptom and maintaining social distancing.

### **Future Vaccine and Research**

Unfortunately, there is no readily vaccine available for COVID-19, though many vaccines are currently under various stages of trials. Many drugs have shown good results on COVID-19 initially, but FDA has not approved use of any of the medicines till now. With increasing number of cases getting reported in India, future research is required to explore the correlation between levels of proinflammatory markers, neuroendocrine changes, psychiatric disorders, and SARS CoV 2 infection. Such research is going to be crucial to sketch the necessity for, if any, future care and support to patients affected with COVID-19.

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