

Research Paper

## Determinants of Anxiety and Depression in Patients with Covid 19 Admitted in a Tertiary Care Hospital of New Delhi, India

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### ABSTRACT

**Background:** COVID 19 pandemic has significantly affected the mental health of patients, especially along with the lockdown crisis. The aim of this study was to assess the prevalence and determinants associated with depression and anxiety among the patients admitted with moderate COVID 19 in our hospital. **Materials and Methods:** It was a cross sectional descriptive study done in 100 admitted cases above 18 years of age. A predesigned proforma was filled along with laboratory investigations in fasting state. Hospital Anxiety and Depression Scale (HADS score) was used for the assessment of mental health of these patients. **Results:** Out of 100 admitted cases with moderate grade severity of COVID-19, the prevalence of anxiety and depression was found to be 31.25% and 47.4% respectively. Both anxiety and depression were found to be associated with low oxygen saturation (less than 85% on room air, higher class of steroids and anticoagulation respectively. Depression was also found to be associated with higher blood sugar and serum creatinine. Anxiety was found to have a direct correlation with high blood sugar, serum transaminases and serum ferritin levels and inverse relationship with use of the drug, ivermectin ( $p < 0.027$ ). **Conclusion:** Our study proves that there is a high prevalence of anxiety and depression in patients with COVID-19. Ivermectin should be a part of treatment of all moderate (or may be mild) cases suffering with this disease.

**Keywords:** Depression, Anxiety, COVID-19, Mental health, Steroids, Hypoxia, Ivermectin

The emergence of a novel form of Coronavirus (2019-nCoV) from Wuhan, China has created a worldwide pandemic and has emerged as a rapidly evolving and a confusing situation. There have been 54 million cases throughout the world out of

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which 38 million have recovered till date. India alone is having 8.8 million cases and 8.2 million recoveries till date. There have been 0.129 million deaths in India and 1.3 million deaths worldwide as reported on 15 November 2020 due to COVID-19. Not only the disease is associated with 2-5 percent mortality, a lot of acute complications like acute myocardial infarction and embolism etc. are seen. Even amongst the patients who survived, late complications including cardiac and pulmonary ones are observed.

Such widespread epidemics are associated not only with physical sufferings but mental health deterioration also. Only a few studies have been done to evaluate the impact of this disease on the psychological status of these patients. In order to address this unseen face of the COVID 19 pandemic, this study was executed.

### **MATERIALS & METHODS**

It was a descriptive cross-sectional observational study which included 100 cases of moderate grade severity of COVID infection amongst adults of more than 18 years of age admitted in COVID wards of a tertiary care center of New Delhi during October 2020.

All cases falling into mild or severe category requiring either home isolation or ICU management were excluded. Similarly, all the cases with past history suggestive of psychiatric illness or neurological disorder, head injury, CNS infection anytime in the past or on psychotropic or antiepileptic drugs were also excluded.

A thorough history and clinical examination with special focus on the social and demographic factors along with relevant laboratory investigations were undertaken. A single observer filled a predesigned social, demographic and clinical proforma along with Hospital Anxiety and Depression Scale (HADS score) for these patients. Appropriate statistical analysis was done accordingly.

### **RESULTS**

A total of 100 cases with moderate COVID 19 infection fulfilling the inclusion and exclusion criteria were recruited. The mean age of the cases was 48.19 years. Amongst all cases, 68.39% were males and 31.7% were females. The overall prevalence of depression was found to be 47.4% out of which 23.4%, 20% and 4% cases were found to have mild, moderate and severe depression respectively. Similarly, the overall prevalence of anxiety was found to be 31.25% out of which 22% and 9.25% had mild and moderate anxiety respectively. No case was found to have severe anxiety as per HADS score.

On analysis, depression was found to be significantly higher in cases with monthly income less than Rs 10,000/- per month ( $p < 0.035$ ), higher level of education i.e., graduation and above ( $p < 0.001$ ), those who were self-employed ( $p < 0.01$ ), and four-wheel vehicle owners ( $p < 0.007$ ). It was also observed that odds of depression were higher in subjects with concomitant comorbidities like diabetes, hypertension, chronic kidney disease, coronary heart disease or bronchial asthma compared to those without any comorbidity ( $p < 0.001$ ). Blood sugar and serum creatinine levels among the subjects with depression were found to be significantly higher as compared to those not having depression ( $p < 0.001$  and  $< 0.016$  respectively). However, no correlation appeared to exist between depression and gender, occupation, family structure (nuclear vs. joint family), duration of disease and duration of symptoms.

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No difference was observed between the prevalence or severity of depression in patients treated with Hydroxychloroquine sulfate, antibiotics, ivermectin and remdesivir. Similarly, no association of depression was seen with poor prognostic laboratory markers like serum ferritin, C-reactive protein (CRP), creatine phosphokinase (CPK) and D-dimer. However, depression was found to be significantly higher amongst the subjects receiving higher doses of steroids [dexamethasone more than 8 mg/day or methylprednisolone more than 32 mg/day ( $p < 0.010$ )] and anticoagulation [twice a day enoxaparin or heparin ( $p < 0.019$ )] and those with lower oxygen saturation (less than 85%) on room air ( $p < 0.006$ ).

In regards to anxiety, no association was observed between anxiety and gender, occupation, family structure, family income, education, employment or type of owned vehicle but the prevalence of anxiety was found to be higher in cases who were on higher doses of steroids ( $p < 0.007$ ), anticoagulation ( $p < 0.001$ ), at rest oxygen saturation of less than 85% on room air ( $p < 0.001$ ) and inversely associated with those who were on ivermectin ( $p < 0.027$ ). Anxiety was also found to be higher in cases with persistent pyrexia ( $p < 0.02$ ), high blood sugar ( $p < 0.016$ ), transaminitis ( $p < 0.01$ ) and higher serum ferritin levels ( $p < 0.02$ ). However no correlation was found between other lab parameter including CRP, CPK, Ferritin and D-dimer with the prevalence or severity of anxiety.

### DISCUSSION

A number of studies have shown increasing prevalence of anxiety and depression in patients with various chronic diseases like coronary heart disease, chronic kidney disease, heart failure, malignancy, diabetes etc.<sup>1-3</sup>. Since COVID-19 is a new disease with very minimal insight into the pathogenesis and sequelae, hence no knowledge is available, especially regarding the mental health status of people infected with this virus. A variety of complications have been linked to COVID-19 and many physical alterations or consequences have been linked to it and are being studied in detail in various ongoing research. However, psychological illness specially anxiety and depression have not been studied vastly, especially in this part of the world.

The proportion of the global population with depression and anxiety in 2015 is estimated to be 4.4% and 3.6% respectively<sup>4</sup>. While the crude prevalence for both depressive and anxiety disorders was 3.3% (3.1–3.6 for depressive disorders and 3.0–3.5 for anxiety disorders) in general population in India itself<sup>5</sup>.

Our study included one hundred cases with active moderate COVID-19 infection, out of whom 47% were found to have depression and 31% had anxiety which is approximately more than ten times the prevalence in general population. This was because of the fear of death, complete isolation from the family and society and future uncertainties (disease related or financial) associated with present times, especially in a developing country like India.

A similar study done in Italy amongst 402 cases with COVID infection reported that 55.7 per cent of COVID-19 affected cases had at least one psycho-pathological manifestation. To enumerate, 28 per cent were found to be suffering with post-traumatic stress disorder, 31 per cent with depression, 42 per cent with anxiety, 20 per cent with obsessive-compulsive symptoms and 40 per cent suffered with insomnia<sup>6</sup>. Current study had similar although lesser prevalence of anxiety because only moderate cases were included in this study as compared to moderate as well as severe cases in Italian study. Hence disease burden

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estimated was lower in current study leading to lesser psychological impact. Apart from that we did not include post-traumatic stress disorder as ours was a cross sectional study, done during hospital stay as compared to the Italian study where subjects were interrogated even after discharge.

The reason behind the psychopathological manifestations in COVID-19 disease is unclear. However, the common postulate is either the direct involvement of central nervous system by the virus or indirect affect through an immune response<sup>7,8</sup>. Along with this, people all over the world are experiencing emotional instability due to lockdowns and discontinuation of daily activities like schools, business, jobs, travel and leisure<sup>9</sup>. Apart from the immune system mechanisms, the fear of the illness, uncertainty of the future, stigma, traumatic memories of severe illness and social isolation may exacerbate the psychological behavior in patients with COVID-19<sup>10</sup>.

In our study depression and anxiety were not found to be associated with gender, occupation, family structure and treatment given in terms of hydroxychloroquine sulphate or antibiotics including antivirals. However, it was seen that patients with lower oxygen saturation on room air had significantly higher prevalence of both depression and anxiety. These patients were given oxygen by high flow nasal cannula or noninvasive ventilation, hence the feeling of being sicker than other patients (admitted in same wards) and impending death might be the reason attributable for being more anxious or depressed. A Chinese study conducted in Wuhan, China on 144 COVID-19 reported the prevalence of anxiety and depression in 34.72% and 28.47% of cases respectively and also found low oxygen saturation ( $\beta = -2.140$ ,  $p = 0.049$ ) to be associated with anxiety in these patients<sup>11</sup>.

Depression and anxiety were also found to be more in cases on higher doses of steroids. Steroids modulate hyper inflammation and inhibit immune responses that are vital for preventing the patients from the fatal cytokine storm in the COVID-19 virus infection. But steroids are also the known culprits to induce psychiatric disturbances including depression. Timing of appearance of symptoms may vary from immediate (at time of initiation) to even after cessation of treatment. Short term steroid treatment as given in cases of COVID-19 can induce delirium or change in mood in up to 52% of the cases however hypomania and mania are commoner than depression<sup>12</sup>. A case series amongst SARS positive patients from Hong Kong stated that the steroids given to combat cytokine storm from SARS virus infection resulted in mild steroid induced psychiatric problems such as depression, anger and anxiety in seventy percent of patients and severe issues like hallucinations, maniac features and suicidal tendencies in rest thirty percent cases<sup>13</sup>. In our study both anxiety and depression were found to be more prevalent in those who were on twice a day anticoagulation. Anticoagulation (enoxaparin or heparin) twice a day was given for cases with higher D-dimer and hence amongst cases with more severe disease. The fear of twice a day subcutaneous painful injection and having severe disease as compared to others who were either on once a day or no anticoagulation at all might be the reason for higher anxiety and depression in these individuals. Also, another reason can be that the patients receiving higher doses of anticoagulation belong to the moderate to severe class of disease. It implies higher inflammatory state that is associated with higher levels of circulating cytokines, which has been shown to be associated with depression and anxiety<sup>14</sup>. Cytokines like IL6, TNF, IL  $\beta$  produce behavioral alterations by influencing neurocircuitry and neurotransmitter systems in brain. Even in acute illnesses, they induce "sickness behavior" that includes depressive symptoms like anhedonia, anorexia, fever, sleep changes, and decreased social

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interaction, by activating the innate immune system. However more studies are needed to answer this fact.

Higher prevalence of depression was also found to be associated with hyperglycemia and raised creatinine levels. SARS-COV-19 is found to act on ACE as well as DPP-4receptors and can cause acute hyperglycemia<sup>15</sup>. Medical audit committee analysis of our own hospital has found significantly higher blood sugar and serum creatinine in patients dying because of COVID-19. They may be because of high viral load or hyper inflammatory state causing organ dysfunction. Cases with COVID-19 with hyperglycemia and high renal parameters not only are found to have higher mortality but longer duration of hospital stay and more complications or need for intensive management. This may explain the higher prevalence of anxiety and depression in these individuals. Apart from that hyperglycemia can by itself cause depression even in non-COVID cases as stated by Nicolos Bolo et al who by inducing hyperglycemia, followed by functional MRI and MR spectroscopy found induction of changes in glutamate levels which was associated with depression in higher concentrations<sup>16</sup>. Similar to our study ZhangJ. et al found higher serum creatinine levels to have significant association with mortality in patients with COVID-19 ( $p < 0.001$ ). Serum creatinine (OR: 2.69, 95%CI: 1.18-6.11) was found to be an independent risk factor for 28-days outcome. Higher serum creatinine suggests severe disease, more inflammation, longer duration of hospital stay, poor outcome and higher morbidity hence associated with depression<sup>17</sup>. This longer hospital stay of COVID-19 because of the associated renal failure or hyperglycemia leads to feeling of sickness, helplessness and loneliness augmenting the chances of depression and anxiety in these individuals.

Anxiety was found to be associated with higher ferritin and serum transaminase levels. Although the most frequent and critical clinical presentation in COVID-19 is secondary to the involvement of the lung (fever, cough), the infection may lead to a systemic disease<sup>18</sup>, also involving the liver and gastrointestinal system<sup>19</sup>. Apart from that, the immune response in COVID-19 infection is of interest and has shown to be associated with a hyperinflammatory state with increased concentrations of C-reactive protein, serum ferritin, and interleukin-6 causing transaminitis or renal failure. The link between inflammation and mental disorders is well described in literature and might explain some of the psychiatric morbidities.<sup>20</sup>

One interesting finding was that treatment with Ivermectin was associated with lower levels of anxiety in these patients, though no association with depression was seen. Ivermectin, a macrocyclic lactone disaccharide, was studied by H de Souza Spinosa et al in lab rats and he found that at doses of 1mg/kg, it showed an anxiolytic effect with GABAergic properties<sup>21</sup>. This probably explains the inverse association of Ivermectin with anxiety as found in our study. Though no studies were done in humans, this is a novel observation in our study that needs further evaluation and research and may have significant treatment implications.

Also, depression was found to be higher in educated people (graduates and above) and those who owned a four-wheeler. It is a known fact that as we move to urban life, chances of depression are more. Living in small nuclear families and with lack of social support (to them or to their family quarantined at home) increases the impact of COVID 19 on their mental status. Depression was also found to be more in self-employed or employees in private jobs and those with monthly income less than Rs. 10000 per month where we can

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presume that the monetary and financial losses due to lockdown and disease associated isolation leading to loss of working days and wages, were higher in these individuals and may be considered catastrophic as compared to those in government jobs, who have fixed permanent salaries.

The results of our study reinstate the fact that COVID-19 pandemic and lockdown has taken a toll on the psychological state of people affected. We are going through third wave in Delhi and presently looking primarily at reduction of mortality in people with COVID-19 but it's a high time to look upon the neglected mental health of these individuals, especially those who are admitted and alone in the wards. A psychiatric assessment of all the patients is the need of an hour.

### *Limitations of the Study*

Although our study is probably the first on subjects with COVID-19 infection from this part of the world, the results cannot be extrapolated to the whole population. The current study recruited only moderate cases and not mild (in home isolation), which constitute the major chunk (more than 80%) of COVID 19 cases. Apart from that we did not perform HRCT chest, IL6 levels and viral load which could have shown better correlation of the disease itself or cytokines with the psychological state.

## CONCLUSION

The long-term impact of COVID 19 on mental health may take months to become fully apparent. There is a need for further research in this arena to augment complete psychiatric management of the affected patients. The current study is a small step in this direction. It shows that patients with COVID 19 disease have significantly higher prevalence of depression and anxiety. Therefore, timely intervention is needed to prevent them from going in a chronic mental disease state. Apart from physicians and critical care specialists, a psychiatrist and a psychologist should be a part of management team for these patients. Ivermectin should be kept as part of management of COVID-19 infection not only to control the disease but also for its observed anxiolytic effects to reduce the chances of anxiety which may lead to long term asthenia and myalgia syndromes. Although steroids and anticoagulation are the backbone therapy for COVID-19 but a close watch should be kept on patients who are on these two medicines specially when used in higher dosages.

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***Conflict of Interest***

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