

## Long term complications and rehabilitation of COVID-19 patients

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### Abstract

With the ongoing pandemic of COVID-19 having caught the world almost unaware millions of people across the globe are presently grappling to deal with its acute effects. Our previous experience with members of the same corona virus family (SARS and MERS) which have caused two major epidemics in the past albeit of much lower magnitude, has taught us that the harmful effect of such outbreaks are not limited to acute complications alone. Long term cardiopulmonary, glucometabolic and neuropsychiatric complications have been documented following these infections. In the given circumstance it is therefore imperative to keep in mind the possible complications that may occur after the acute phase of the disease subsides and to prepare the healthcare system for such challenges.

**Keywords:** COVID 19, Long Term Complications, Cardiopulmonary, Glucometabolic, Neuropsychiatric.

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### Introduction

In December 2019, an aggressive and atypical viral pneumonia was described with its origin epidemiologically pin-pointed to Huanan seafood market in Wuhan, China.<sup>1</sup> A new human-infecting virus of the coronavirus family was subsequently identified with the use of next-generation sequencing, which was provisionally named 2019 novel coronavirus or COVID 19 (2019-nCoV). Till the date of writing this article almost 27,00,000 individuals have been infected by the virus and around 1,90,000 people have succumbed to it with the case fatality reported to be close to 5%. There have been 2 previous outbreaks of coronavirus epidemics, namely, severe acute respiratory syndrome (SARS-CoV) in 2003 and Middle East respiratory syndrome (MERS - CoV) in 2012 caused by SARS and MERS viruses,

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**Table-1:** Probable long-term complications of COVID-19.

#### A. Cardiorespiratory Complications

1. Cardiovascular Complications-
  - \*Increased Cardiovascular Disease
2. Pulmonary Complications-
  - \* Intralobular and Interlobular Septum Thickening
  - \* Impaired FEV 25-75
  - \* Reduced Diffusion Capacity

#### B. Glucometabolic Complications

1. Increased Risk of Dyslipidemia
2. Increased Risk of Hyperglycaemia
3. Endocrinological Complications
  - \*Hypocortisolism
  - \*Primary and Central Hypothyroidism

#### C. Neuropsychiatric Complications

1. Neuromusculoskeletal
  - \*Persistent Musculoskeletal Aches and Pains
  - \*Femoral Head Necrosis
2. Psychiatric Complications
  - \*Depression
  - \*Post-Traumatic Stress Disorder
  - \*Somatoform Pain Disorder
  - \*Panic Disorder
  - \*Chronic Fatigue Syndrome
  - \*Compromised Quality Of Life

respectively. Although, the scale of morbidity and mortality noticed in the previous corona virus epidemics does not match the ferocious and unprecedented havoc induced by ongoing COVID19 pandemic. Genomic sequence studies of COVID-19 have shown that this virus has nearly 50% and 77% similarity to MERS-CoV and SARS COV respectively.[2 Like the SARS-CoV-, the SARS-CoV-2 also binds to Angiotensin converting enzyme (ACE)2 to gain entry to its host cell receptor, although it has a higher binding affinity for ACE2 as compared to the former.

We are amidst an acute healthcare crisis evoked by highly pathogenic nature of COVID19 with precious resources of even advanced economies being stretched to the hilt. On the same account, it is of utmost importance to fathom the potential long-term complications of this novel virus so that healthcare systems are geared up to meet up such challenges in

not so distant future. Keeping in mind the structural as pathogenic mechanistic similarities between the 3 viruses of the corona family, it is perfectly reasonable to assume that the long-term complications of Covid 19 pandemic should be on similar lines as its 2 predecessors (although at a much higher magnitude). The expected long-term complications can be divided into three sub-groups, namely — the cardiorespiratory, glucometabolic and neuropsychiatric complications (Table-1).

### Cardiorespiratory Complications

**Cardiovascular (CVD) Risk** — The viruses of corona family induce a significant systemic inflammatory response along with localized vascular inflammation leading to an increased risk of myocarditis and thromboembolic events during the acute-phase of illness.<sup>3</sup> On the other hand, the long term sequelae associated with these group of viruses on cardiovascular system are less well understood at this point of time. In a study, hospitalization with pneumonia (not SARS) was associated with subsequent increase in the risk of CVD which remained approximately 1.5-fold higher after the first year despite adjustment of confounding risk-factors. Certain hypotheses have been put forward to explain the increased risk including pro-inflammatory changes in the cellular composition of the atherosclerotic lesions, persistent systemic inflammatory activity, high circulating inflammatory markers, persistent pro coagulant state with higher levels of coagulation markers and persistence of dysfunction in organs such as kidneys which can directly or indirectly impair the CVD parameters.<sup>4</sup>

### Pulmonary Complications

The clinical and radiological imaging features of novel coronavirus disease 2019 (COVID-19) on pulmonary system reported so far show "significant overlap" with those of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).<sup>5</sup> Based on it, one can extrapolate the respiratory sequelae of COVID19 should be on similar lines as seen on long-term follow up of individuals afflicted with SARS and MERS viruses. The Computed Tomography (CT) scan images of individuals affected during the previous epidemics (SARS and MERS) have shown ground glass opacities (GGO) being the dominant radiological lesions at 6 months (from point of infection). Interestingly, intralobular and interlobular septum thickening were more prominent radiological features when these individuals were re-evaluated at 84 months.<sup>6</sup> Indices of pulmonary function in SARS survivors admitted to

intensive care unit (ICU) were noticed to be inferior to those treated in medical wards, though no significant differences were found for other indices like 6 minute walk distances and respiratory muscle strength.<sup>7</sup> A 15-year follow up from a prospective cohort study of SARS recovered patients from 2003 to 2018 showed improvement in pulmonary function tests and radiological parameters in CT during the first year post-illness. The pulmonological improvement plateaued during the subsequent years with around 40% and 38.5% individuals having persistent impaired.

FEF 25%-75% and diffusion capacity respectively at the end of 15 years.<sup>8</sup> These studies highlight the importance of long term follow up of survivors specially for the individuals who developed moderate to severe acute respiratory disease. The clinicians should evaluate clinical functional respiratory parameters apart from considering formal pulmonary function testing on follow up visits. Chest physiotherapy and functional rehabilitation could help alleviate morbidity in individuals with residual pulmonary functional impairment.

### Glucometabolic Complications

#### Risk of Dyslipidaemia

An observational study which analysed the lipid metabolism parameters in recovered SARS patients 12 years after the initial acute disease, noticed a rise in triglyceride and very-low density lipoproteins (VLDL) levels apart from a significant rise in the levels of serum metabolomes, namely phosphatidylinositol and lysophosphatidylinositol (LPI). Dyslipidaemia was noted in 68% of the survivors as compared to 40% of the healthy volunteers.<sup>9</sup> The clinicians involved in long-term rehabilitation of individuals afflicted with moderate to severe COVID-19 infection should remain mindful of potential increased risk of dyslipidaemia in this cohort of patients. Lifestyle modification including a balanced diet and regular exercise remains the cornerstone of improving long term metabolic outcomes. LPI has been found to have roles to play in the excitability of dorsal root ganglion neurons, intestinal inflammation, and the migration and orientation of human breast cancer through G-protein coupled receptor 55 expressed in these tissues which could perhaps explain various symptoms observed in the recovered SARS patients.

#### Risk of Diabetes

Abnormal glucose metabolism has been reported in 60% of post SARS survivors as compared to 16% of controls. Alteration in various biochemical parameters such as

hyperinsulinemia, insulin resistance and hyperglycaemia has been reported in a significant proportion of recovered SARS patients. An association between Lysophosphatidylinositols (LPI) and glucose metabolism in recovered SARS patients has been suggested as a possible pathogenic mechanism. LPI is believed to play a critical role in glucose homeostasis based on their action on insulin release with G-protein coupled receptor 55 (GPR55) potentially being an important factor.<sup>9</sup> Increased rate of glycolysis has been observed in the recovered SARS patients. There have been reports of islet cell damage by SARS-CoV,<sup>10</sup> although the long-term sequelae of these viruses on pancreatic islet cell function has not yet been studied.

### Endocrinological Complications

Use of high doses of corticosteroids during the acute infection phase of SARS can lead to subsequent hypocortisolism. However, assessment of endocrinological parameters of SARS survivors at one year has revealed the presence of hypocortisolism in around 39% individuals even in the absence of steroid use in around two-thirds of the studied population. This response has been attributed to be a delayed pathological complication of SARS.<sup>11</sup> The hypocortisolism could possibly explain the persistence of symptoms seen in post SARS patients such as apathy, lethargy, malaise, fatigue, weakness, orthostatic dizziness and anorexia.<sup>12</sup>

Based on observational data in SARS and MERS survivors, it is imperative that individuals with moderate to severe COVID-19 infection be evaluated clinically for potential dysfunction of adrenocorticotropin hormone (ACTH)-cortisol axis specially if the above-mentioned symptoms are present. Measurement of 9 am cortisol and a dynamic hormonal challenge testing (short synacthen test) should be carried out, if clinically warranted. An explanation put forward to explain the hypothalamic-pituitary-adrenal (HPA) axis dysfunction, considers it as a generic, transient adaptive physiological response to the prolonged activation of the HPA axis during the acute phase of the disease. This school of thought advocates against using supplementary steroids in such individuals considering this response to be an adaptive physiological state to conserve energy.<sup>11</sup> In a study of 61 survivors of SARS, hypothyroidism was observed in 7% of the individuals.<sup>12</sup> Histopathological studies have shown distortion, dilatation, and collapse of follicular and parafollicular architecture, apoptosis, and fibrosis.<sup>13</sup> Hypophysitis causing central hypothyroidism has also been postulated as a possible pathogenic mechanism

specially considering the identification of genome sequences of the virus in the hypothalamus and cortex of the brain during the acute stage of the disease.<sup>14</sup> Subacute thyroiditis is also a condition which needs to be kept in mind given its close association with viral infections. There have been reports of drug interaction between Lopinavir/Ritonavir combination (used as part of research treatment protocols) with levothyroxine in patients with COVID-19. Patients who are on levothyroxine therapy may experience a rise in TSH levels when given above mentioned anti-viral therapy.<sup>15</sup> Keeping the complex and hitherto unknown impact of COVID-19 virus on thyroid gland function, all survivors of moderate to severe COVID-19 infection should be clinically and biochemically evaluated for potential thyroid gland dysfunction during follow-up visit.

### Neuropsychiatric Complications

#### Neuromusculoskeletal Complications

Persistent neuromuscular abnormalities have been observed amongst survivors of SARS. In a study involving 128 health care workers with musculoskeletal complaints -2-years after the SARS outbreak it was seen that difficulties in performing activities of daily living and work tasks persisted in the patients despite receiving acute rehabilitation measures.<sup>16</sup> It has been suggested that bringing in force outcome measure assessment tools which allow patients to identify specific limitations or address overall health related quality of life (such as the SF-36)<sup>17</sup> may be helpful for the measurement of subjective improvement and thereby in planning proper rehabilitation measures. Femoral heads necrosis has been reported in SARS patients which however unlike necrosis caused by other conditions such as long-term steroid use or leukaemia, remains stable and even spontaneously reverse.<sup>8</sup>

#### Psychiatric Complications

Psychiatric morbidities, chronic fatigue and resultant functional disabilities have been persistently noted to be high and clinically significant amongst SARS survivors. A 4-year study of SARS survivors has shown that active psychiatric illnesses was reported in more than 40% and chronic fatigue was reported by 40.3% (while 27.1% met the criterion for modified 1994 Centers for Disease Control and Prevention criteria for chronic fatigue syndrome.<sup>18</sup> Another study reported high incidence of depression, post-traumatic stress disorder, somatoform pain disorder, and panic disorder in SARS survivors after 3 years.<sup>19</sup> Interestingly a trend of progressive rise in psychiatric morbidities has been noted after the event which continued to increase with

the passage of time. Assessment by standardized questionnaires showed figures around 10% to 35%<sup>20</sup> in the acute phase of the infection (acute stage to 1 month) that increased to 64% at 1-year follow-up.<sup>21</sup> A role of immunological dysfunctions, including cytokine disturbances has also been suggested.<sup>22</sup> During acute SARS infection, cytokine storm has been demonstrated and prospective studies among survivors will be needed to clearly understand their long-term role in such conditions. Alterations in the insertion/deletion (I/D) polymorphism in the ACE gene have been associated with increased risk of chronic fatigue syndrome and as SARS-CoV utilizes the angiotensin-converting enzyme-2 ACE2 as a portal of cellular entry that could be a link in the explanation of association between SARS and chronic fatigue syndrome.<sup>23</sup> In view of the high figures of long-term psychiatric dysfunction, it is important to optimize the diagnosis and treatment of mental health morbidities by a multidisciplinary approach aimed at long-term rehabilitation. Adequate measures to dispel perceived social stigmatization and proper functional rehabilitation would have strong roles to play in this context.

Apart from these complications an association between COVID 19 and a rise in cancer biomarkers like CYFRA21-1 and HE4 have also been noted which raise an alarm of potential malignancy in the future and need follow up.<sup>24</sup>

## Conclusion

Although the COVID 19 virus was only reported for the first time in December 2019, it has already transcended continental borders posing catastrophic threat to healthcare systems and global economies during the acute phase of illness. The long term implications of Covid19 infection on morbidity and mortality are yet unknown although some basic deductions can be made based on clinical experience gained from residual long term effect of SARS and MERS epidemics.

**Table-2:** List of recommendations to identify and treat the anticipated long-term complications of COVID 19.

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| 1. Clinical Screening for Symptoms Of Cardiovascular Complications, Neuromuscular Complications, Thyroid Disorders, Standardised Questionnaires For Assessment of Psychiatric Status. |
| 2. Laboratory Investigations-Blood Sugar, Lipid Profile, Thyroid Function Tests, Se Cortisol (If Clinically Indicated), Pulmonary Function Tests                                      |
| 3. Adaptation of Healthy Lifestyle Measures   |
| 4. Rehabilitation Measures Like Chest Physiotherapy, Psychiatric Counselling, Functional Rehabilitation   |

As the magnitude of covid19 pandemic is at an unprecedented scale, we can anticipate a far higher surge in cardio-pulmonary dysfunction and neuropsychiatric sequela in the survivors of this highly pathogenic novel corona virus. The experience gained from observed long term impact of related viruses from the HuCoV family in both the physical and psychological domains, could be used as a handy checklist while planning rehabilitation of COVID19 survivors (Table-2). Early signal emerging from this pandemic suggests an increased case-fatality in individuals with multiple metabolic co-morbidities including obesity, hypertension and diabetes. This once again reinforces the importance of lifestyle measures such as regular exercise and healthier diet to be adapted at individual, family, and social level to mitigate the impact of pandemics in future.

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