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MINI-REVIEW

Association of Circadian Clock and Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing devastation worldwide accounting millions of deaths. This virus is among the new member of the *Coronaviridae* family with differences from SARS-CoV. The entry of the virus to human cells mediated through spike (S) proteins with angiotensin-converting enzyme 2 (ACE2). Several comorbidities such as hypertension, diabetes, HIV, malignancy, diabetes, chronic respiratory disease, and cardiovascular disease makes a person susceptible to COVID-19 infection. Circadian rhythm/oscillations or biological clock plays important role in the pathogenesis of SARS-CoV-2 infection mediated through ACE2 and BMAL1.

Key Words: Severe acute respiratory syndrome coronavirus 2; Hypertension; Diabetes mellitus; Circadian rhythm; Oscillations

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family of *Coronaviridae* and has similar properties like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) [1]. The primary host is believed to be a bat as the genome sequence of SARS-CoV2 has high complementarity (90%) with bat coronavirus while the intermediate host between bat and human was most probably a Himalayan civet [2]. The first clustered cases of COVID-19 were reported on 31 December 2019 in people associated with the wet market in Wuhan, China where live or slaughtered animals were sold [3]. On 11th March 2020, WHO declared this as pandemic disease. From the first day of its occurrence, it took less than 3 months to cross the figure of 500,000 cases worldwide [4]. This tremendous spread of this disease is mainly because of its high sustainability on non-living things, i.e., for more than 72 hours. Currently, there are 153,094,318 confirmed cases with 3,206,339 confirmed deaths from 197 countries. The mean period of occurrence of symptoms is 5.5 days and it may be possible that a high number of undiagnosed cases without any symptoms will be there who are spreading the disease unknowingly [5,6]. Some studies have projected a high number of cases which can create serious havoc [7]. Currently, the most affected part of the world in the current scenario is USA & European provinces with the maximum number of deaths reported from Italy (15,362 deaths) [8] and Spain (11,774 deaths) [9].

PATHOGENESIS OF SARS-CoV-2 INFECTION

The disease spreads through the mucous and faecal medium [10-12]. It has similar pathogenic action as that of SARS-CoV [13,14]. The virus comprises two types of spike protein (S protein) all over its membrane which helps it in binding with the host cell [15,16], an envelope protein (E protein) and membrane protein (M protein) form the capsid of the virus. Single-stranded positive RNA is the genetic material of this virus [17].

SARS-CoV2 also uses angiotensin-converting enzyme 2 (ACE2) receptors of type 2 cells of alveoli like SARS-CoV for interaction

with host cells. Transmembrane protease serine 2 (TMPRSS2) is needed for S protein priming [13]. There are two types of S protein, i.e., S1 and S2 which participate in binding and fusion, respectively. S1 binds with the ACE2 receptor while S2 mediates fusion between virus and host cell [18]. Once the virus enters the host cell, it shreds its protein part and RNA is released into the cytoplasm. The ssRNA(+) uses host mechanism to translate into two polypeptides, i.e., PPa1 and PP1ab which form a replication transcription complex. Further, the formed complex uses RNA dependent RNA polymerase to replicate and make multiple copies. Finally, it gets assembled into its virion vesicles and fuses with plasma membrane and gets released. It spreads down the bronchial tubes and starts infecting neighbor cells. The accumulated proteins of virus, dead type 2 cells of alveoli attract macrophages and cytokines as an immune response and result in inflammation. This further results in the filling of lungs with water and dead cells causing acute respiratory disease [19-21].

MORBIDITIES IN SARS-CoV-2 INFECTION

SARS-CoV-2 is known worldwide pandemic infect people of all age groups; however, persons above the age of 60 years with comorbidities like hypertension, diabetes, HIV, malignancy, diabetes, chronic respiratory disease, and cardiovascular disease (CVD) are more susceptible to infection [22]. People having diabetes mellitus (DM) are susceptible for getting COVID-19 infection due to their impaired phagocytic cell characteristics. In one of the recently published study, it was found that DM people have significantly high levels of ACE2 receptors, this might prejudice people with DM to SARS-CoV-2 infection [23]. Recently collected data showed that 11–58% with COVID-19 infection have DM with 8% fatality rate [24,25].

Obesity

Obesity (body mass index >30 kg/m^2) is associated with low oxygen saturation of blood as suggested by the recently published study [26]. Obesity is among the mild associated comorbidities in COVID-19 infections. Previously published literature showed that 47.6% obese people showed SARS-CoV-2 infection among them 68.6% was on ventilators because of critical conditions [26]. Thus, it is proposed that BMI is a risk factor for COVID-19 severity.

Chronic obstructive pulmonary disease

COVID-19 severity is also found to be associated with the chronic obstructive pulmonary disease (COPD). In previously published study, COPD and other chronic disorders were found to linked with SARS (1.4%) and MERS (13%) [27]. It has been observed that around 50−52.3% subjects of COPD admitted to intensive care unit (ICU) having COVID-19, this is because of the microenvironment changes in lungs, blockage of air passages due to increase in mucous secretion [28].

Asthma

It is observed that patients with asthma shows delayed innate antiviral immune response due to impaired secretion of interferon (IFN)-λ. In previously published study, SARS and MERS affected population of 1.4% and 13% respectively showed association with asthma [27]. It is believed that asthma could be the major risk factor for the SARS-CoV-2 infection. In one of the previously published study, it was found that asthma is not associated with COVID-19 disease; however, asthmatic smokers showed direct association with SARS-CoV-2 infection [29].

Hypertension

Hypertension is a potent risk factor in various diseases. Uncontrolled blood pressure is found to be associated with COVID-19 and high case fatality rate (CFR). In one of the recently published Chinese study, it was found that 23% hypertensive subjects showed 6% CFR [30]. The pathophysiology of this association is linked with ACE2 inhibitors. In the treatment of hypertension, the ACE2 inhibitors and angiotensin receptor blockers are frequently used targets for the treatment. Moreover, elevated amount of these inhibitors, upregulate the expression of ACE2 receptors, thereby putting on high risk for SARS-CoV-2 infection [31]. The management of hypertension is essential part in COVID-19 patients that might also be helpful in reducing the disease burden and morbidity.

CVDs

CVDs is strongly associated with SARS and MERS infection. In one of the previously published study, CVDs showed 8% and 30% significant association in SARS and MERS patients, respectively [32,33]. In another study, it was found that 17% of the COVID-19 non-survivors had CVDs [34]. However, the mechanism underlying such morbidities is not known, but most of the COVID-19 patients with CVDs reported compromised immune system [24]. In another research, it was found that increased levels of inflammatory cytokines in COVID-19 is a potent risk factor for development of atherosclerosis, pro-coagulant initiation, and hemodynamic instability that is responsible for ischemia and thrombosis [35].

Moreover, some of the other potential risk factors associated with co-morbidities in COVID-19 patients includes, HIV, malignancies, liver diseases, and other immune system related disorders. Management of the SARS-CoV-2 infected subjects should focus on treatment of all comorbidities related to COVID-19 disease.

ROLE OF CIRCADIAN RHYTHM IN PATHOGENESIS OF SARS-CoV-2 INFECTION

Circadian rhythm or biological clock plays important role in the pathogenesis of SARS-CoV-2 infection. In COVID-19, ACE2 plays anti-inflammatory role upon hydrolysis of angiotensin 2 into angiotensin 1−7. In one of the recently published study conducted one older individuals, which are at higher risk of COVID-19 de-

velopment, it was found that there is significantly lower levels of ACE2 and angiotensin 1−7 levels [36]. SARS-CoV and SARS-CoV-2 have strong similarity as evident by both in-vitro and in-vivo studies that is dependent on the ACE2 recognition, that serve as the entry point for the virus. Several studies demonstrated that circulating renin-angiotensin system showed circadian rhythmicity [37,38]. In one of the study, it was concluded that ACE2 expression followed circadian pattern and it has been stated by the authors that time of day of viral encounter may significantly influence the COVID-19 entry and replication mechanism [39]. Viral clearance within the body exhibit circadian oscillations as concluded by recently published study [40].

Hypoxemic respiratory failure is major cause of death in COVID-19 that involves circadian rhythm and molecular biology of gene expressions involved in it. It is evident that cellular oxygenation actively influence the circadian clocks by the process mediated through hypoxia inducible factor 1 alpha [40]. In another study, alteration in the circadian clock regulated gene expression causes respiratory failure in COVID-19 particularly in lungs thereby causing acute lung injuries [41]. SARS-CoV-2 infection causes expression of the cytokines involving transcription of the cytokines encoding genes that causes stimulation of cytokines release in time-of-day regulation. It is evident that clock proteins and clock genes activate and suppress several cytokines [42]. In another study suppression of type 1 IFN responses were observed in mechanically ventilated COVID-19 patient [43]. SARS-CoV-2 infection is affected by the patient's circadian clock system through two mechanism 1) by direct viral replication within the host's cells and 2) by indirect effects on innate and adaptive immune responses. In one of the previously published study, it was found that BMAL1 have direct effect on circadian oscillations in mouse herpes virus infection [44]. It was concluded by the authors that circadian clock machinery is regulating the angiotensin mechanisms especially ACE2 that is correlated with the SARS-CoV-2 infection [45].

Circadian clock also have strong association with delirium. It was found that about 30% ICU admitted COVID-19 patients have increased risk of developing delirium due to direct central nervous system (CNS) invasion, CNS mediated inflammatory responses and other factors [46]. In basic research it was evident that circadian clock and delirium infection have strong association [46].

CONCLUSION

Considering the several aspects of COVID-19 infections, circadian oscillations and biological clocks have strong association. The factors such as obesity, asthma, hypertension, CVDs poses threat to COVID-19 patients causing significant morbidities in SARS-CoV-2 infected patients. Circadian clock proteins and genes play vital role in regulation of pathogenesis behind the COVID-19 infection. However, limited attention on circadian rhythmicity and biological clock in COVID-19 patients causing delay in recoveries and posing threat towards mortality of these infected patients. Focusing of the circadian clock, may helpful in reduction of the severity of the COVID-19 infection and knowledge of state of circadian proteins and genes may be used to mitigate the COVID-19 severity.

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Conflicts of Interest

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Author Contributions

Conceptualization: Alok Raghav. Data curation: all authors. Formal analysis: all authors. Investigation: all authors. Methodology: all authors. Project administration: Alok Raghav. Resources: all authors. Software: all authors. Supervision: Alok Raghav. Validation: Alok Raghav. Visualization: Renu Tomar. Writing—original draft: Renu Tomar. Writing—review & editing: Alok Raghav.

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