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REVIEW ARTICLE

# Role of Associated Co-morbidities in Severity of Covid-19 Infection: A Systematic Review

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**Abstract**

It is well known fact that people with metabolic disorders were more prone to get any kind of infection because of their weakened immune system. This makes viral entry more accessible into the human hosts and reduces the capability to defend against infection. During this COVD-19 pandemic, older population or population with metabolic disorders were at more risk of getting this infection and eventually leads to their death. The current systematic review scrutinizes the studies done on Covid-19 patients in order to determine the association of co-morbidities as a risk factor in severity of Covid-19 infection.

To conduct a systematic review, electronic databases like PubMed or PMC and Google scholar were searched to appraise studies related with COVID 19 and co-morbidities. We further explored the role of ACE2 enzyme which is important for viral entry into the human host. Herein, we find that people with metabolic disorders viz. diabetes, cardiovascular diseases and/or chronic kidney diseases are at extreme risk of Covid-19 infection. The plausible mechanism is the alteration in the expression of ACE2 enzyme/receptor which promotes the viral entry. Metabolic disorders are major risk factors for disease development and prognosis and therefore severity of Covid-19 infection.

**Keywords:** ACE2, Cardiovascular diseases, Chronic kidney diseases, Covid-19, diabetes, Metabolic disorder

The Coronavirus disease 19 or COVID-19, a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019 and has since then spread across 216 territorial regions as per the World Health Organization (WHO). As per WHO statistics, the total number of cases reported as of on September 29, 2022 globally are 621,878,451 with deaths marking up to 6,545,469. Coronaviruses (CoV) which belongs to subgroup of beta-coronaviruses are enveloped viruses with positive-sense single-stranded RNA genome. They are known to cause mild to severe respiratory infections in humans. Bats are likely the major natural reservoirs of CoV-2 (Shereen *et al.*, 2020). Formerly, two Corona viruses outbreaks are reported that were highly pathogenic, first one have occurred in 2003 in Guangdong province, China, known as severe acute respiratory syndrome (SARS) and second as Middle East respiratory syndrome (MERS) in Middle Eastern countries a decade later. It has been seen that both the viruses are phylogenetically related to CoV-2 and hence show many affinities to its pathogenicity and clinical course(Muniyappa and Gubbi, 2020).

The severity of Covid-19 is based on clinical courses and infectivity. The patients can be categorized on this basis like majority of patients have mild symptom including fever, dry cough, muscle ache, sore throat, runny nose, chest pain, nausea and vomiting. More complicated symptoms include breathing difficulties (dyspnea), ARDS, acute cardiac injury, and multiple organ failure in extreme cases (Wang et al., 2020). Despite of this, some laboratory features were similar as SARS like Lymphopenia (CD4 and CD8 lymphocytes depletion), lengthen prothrombin time and elevation in biomarkers like creatinine kinase, C-reactive protein, D-Dimer, alanine transaminase, lactate dehydrogenase etc. (Wong *et al.*, 2003)(Hui, 2020).

Most of the studies conducted on Covid-19 showed that people with any co-morbidity were more susceptible to the novel CoV-2 because of their weakened immunity. The first study on 41 covid-19 patients was reported by Huang and his team, they investigated that 13 out of them were diabetic, hypertensive, coronary and obstructive pulmonary patients (Huang *et al.*, 2020). A recent study conducted on 1482 hospitalized patients infected with Covid-19 carried out in the United States revealed that 12% of the total cases had history of co-morbidities and including Diabetes (28.3%),

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hypertension (49.7%), obese (48.3%), chronic kidney disease (CKD) (34.6%) and Cardiovascular disease (CVD) (27.8%) (Garg *et al.,* 2020). Similarly, 48% of 191 Covid patients in Wuhan had association with co-morbidities out of which 30% were hypertension, 19% were diabetic and 8% had coronary disease (Zhou *et al.,* 2020). Zhang and his colleagues reported 140 patients from Wuhan infected with Covid-19 out of which 30% were hypertensive and 12% were diabetic (Zhang *et al.,* 2020). This offers a major advantage for virus to attack people with lower or weakened immunity and herein we performed a systematic review to critically appraise the studies done on Covid-19 patients to determine the association of co-morbidities in severity of Covid-19. Along with this, we will criticize the role of angiotensin converting enzyme (ACE 2) which acts as a host receptor for viral entry.

**Search Strategy**

The PubMed database of the National Center for Bioinformatics Information (NCBI) and Google Scholar has been used to search relevant literatures. The relevant studies dealing with COVID-19 patients associated with diabetes along with mortality or co-morbidities were searched in these databases. The literatures were searched using following keywords viz. COVID-19, SARS-CoV, Corona virus, Diabetes, type II diabetes (T2D), Diabetes Mellitus (DM), Obesity, Cardiovascular disease (CVD), chronic kidney disease (CKD), hypertension, clinical characteristics, clinical features, clinical outcomes, drugs, management etc. Those studies were searched which were conducted during the duration of COVID- 19 pandemic period starting from December 2019.

**Development of protocol**

To conduct the systematic review, firstly, a standardized protocol was developed before the including methodology to search relevant data, critical appreciation of those studies followed by an outcome of the study (Fig.1). There were certain inclusion and exclusion criteria which helped in refining of the relevant studies. The inclusion criteria were: (i) retrospective or observational cohort studies; (ii) history of metabolic disorders; (iii) studies describing SARS, MERS or SARS-CoV 2 infections. The studies excluded from this systematic review: (i) literatures does not have sufficient clinical data; (ii) similar studies from the same institution.

**Pathophysiology of SARS- CoV 2**

The viral entry into the human host is always an important aspect to be considering while studying its pathology, mechanism, infectivity or in order to determine the pharmacological sites to target the virus. It is very well known that Spike (S) protein, located on the viral envelop, plays a vital role in the infection. It is glycoprotein having two subunits, first recognizes the host receptor while the latter one being highly conserved helps in viral attachment and fusion with the membrane (Huang *et al.,* 2020). The cellular entry along with fusion with the host cell is a convoluted mechanism involves two important steps: receptor binding and proteolysis (Yan *et al.,* 2020). The mechanism of invading host cell by the virus is similar as that of SARS- CoV where transmembrane angiotensin converting enzyme (ACE2) serves as a host receptor as shown in fig. 2. In both cases, S protein on the viral membrane is the primary

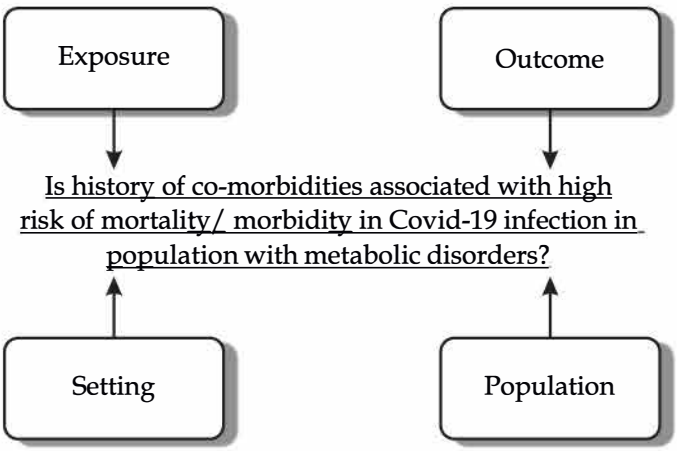


**Fig.1. Flow chart to summarize the methodology for the current systemic analysis**

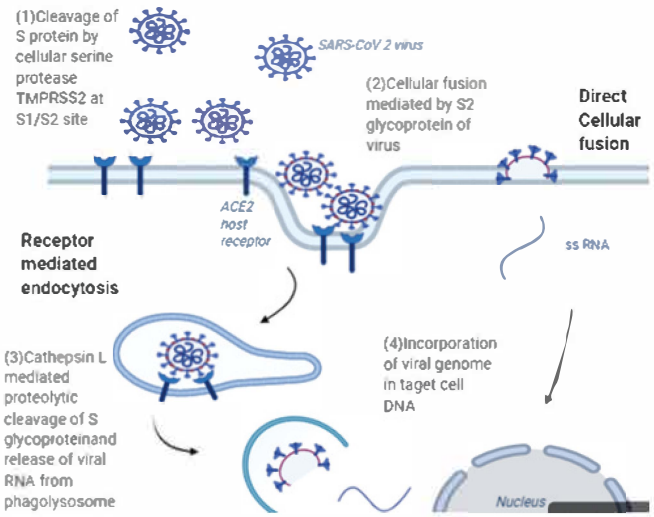


**Fig. 2. Mechanism for cellular entry of SARS-CoV2 into host cell**

determinant for host tropism and pathogenicity (Zhou *et al.,* 2020). It has been seen that interactions between hemagglutinin residues present on virus surface with sialic acid residues on host cell surfaces enhances the binding affinity. Klausegger *et. al.* reported that hemagglutinin-esterase (HE) may constitute a key virulence factor for binding and invading the host cell (Klausegger *et al.*, 1999).

ACE2 is an enzyme highly expresses in pneumocytes and enterocytes and is expressed on the cellular membrane of these cells where it provides a gateway for entry of virus in humans to establish infection. Furthermore, it is also expressed on cardiac cells and vascular endothelia, which may explain cardiovascular complications in some patients (Zhang *et al.,* 2020). Its higher expressions may prove beneficial in providing immunity against SARS-CoV2 invasion as virus may have to with angiotensin-2 protein, a substrate for ACE2 for cellular binding and entrance. Studies had shown that ACE2 expression is much higher in children and young women. It is inversely proportional to the age factor as it tends to decrease with age and chronic conditions like diabetes, hypertension or chronic kidney diseases. So, comparatively raised ACE2 expression in young individuals especially women and those without any chronic co morbid conditions interprets higher protective immunity against Covid-19 (Felsenstein *et al.,* 2020).

**Diabetes as a Risk Factor**

In diabetes, there has been a clinically established linkage between sensitivity to any infection and a weakened immune system. Communicable infection especially spread by respiratory droplets like influenza and pneumonia seemed to be more common and lethal in older age population with type 2 diabetes mellitus (T2DM) (Li *et al.,* 2019). Hyperglycemia have been reported as an important prognosticator of severity and casualties in patients affected with viral infection like pandemic influenza A (H1N1), SARS-CoV and MERS-CoV (Schoen *et al.,* 2019) (Yang *et al.,* 2006) (Banik *et al.,* 2016). Another study shows that low-grade chronic inflammation in diabetic people aides the cytokine storm resulting in severe cases of Covid-19 pneumonias and eventually leads to death of many patients. Also, Interleukin-6 (IL-6), among the different inflammation markers viz. fibrinogen, C-reactive protein or D-dimer has been found to be elevated in Covid-19 cases with diabetes (Maddaloni and Buzzetti, 2020). Many studies have also shown that SARS-CoV-2 infection provokes higher stress conditions, releasing great amount of hyperglycemic hormones e.g., glucocorticoids and catecholamines, leading to increased blood glucose levels and abnormal glucose homeostasis (Wang *et al.,* 2020). Insulin administration known to attenuates ACE2 expression whereas hypoglycemic agents' namely glucagon-like peptide-1 (GLP-1) agonists (liraglutide) and thiazolidinediones (TZDs; pioglitazone), antihypertensives such as ACE inhibitors and statins upregulate ACE2. Therefore it indicates the higher susceptibility of diabetic and hypertensive patients to the virus (Wösten-Van Asperen *et al.,* 2011).

**Cardiovascular Disease as a Risk Factor**

Cardiovascular disease (CVD) comprises of variety of conditions that involve narrowed or blocked blood vessels ultimately affecting heart. This can leads to severe conditions like myocardial infarction, angina pectoris or stroke. A meta-analysis study conducted on ICU vs. non- ICU patients suggests that myocardial injury is 13 folds higher in ICU/severe patients. A CVD patient detected with Covid-19 infection has poor cardiac reserve due to unstable angina or ST-Elevation Myocardial Infarction (STEMI) and has lower tolerance to severe pneumonia. Therefore risk of cardiac insufficiency is much higher in such patients due to array of possible mechanisms (Li *et al.,* 2020). When it comes to contributory mechanisms, it is believed that systemic pro-inflammatory cytokine responses, known to be a mediator of atherosclerosis precisely subsidize to plaque rupture through local inflammation, induction of procoagulant factors, haemodynamic changes and anticipate ischaemia and thrombosis. Angiotensin converting enzyme 2, the receptor for SARS-CoV-2, is also expressed on myocytes and vascular endothelial cells showing theoretical potential possibility of direct cardiac involvement by the virus (Zhou *et al.,* 2020).

Hypoxemic state (low oxygen availability at tissue level) due to breaching of respiratory system by the virus reduces the amount of energy by cellular metabolism eventually raises anaerobic fermentation. This stimulates intracellular acidosis and oxygen free radicals to eradicate the phospholipid layer of cell membrane, influx of calcium ions injury and apoptosis of cardiomyocytes. Further, repeated flow of catecholamines due to anxiety and the after effects of medication can also lead to myocardial damage (Li *et al.,* 2020). It has been seen that drug induced toxicity could be one of the possible cause of cardiac complications worsening of condition in chronic cardiac patients infected with Covid-19. Chloroquine and its derivative hydroxychloroquine have been reported to cause side

effects that include impaired conduction and hypertrophic cardiomyopathy. Other drugs used for Covid treatment like immunomodulator interferon alpha and antiviral agent Ribavarin may also cause some damage to the heart (Wang *et al.*, 2020).

Increased risk of Myocardial Infarction, blood pressure abnormalities, palpitations due to arrhythmia, reduced ejection fraction and consequent cardiac hypertrophy are observed after recovery from illness in patients with existent cardiovascular diseases. Long term effects due to Covid-19 infection must be investigated in such patients and probability of heart failure examined (Zaim *et al.*, 2020).

**Chronic Kidney Disease as a Risk Factor**

Chronic Kidney disease is a long term exposure where either they are damaged or cannot function properly. As per a meta-analysis done to find out prognosis and severity of Covid-19 in patients with liver and kidney diseases, the rate of mortality in Covid-19 patients with CKD and liver diseases was found to be 53.33% (8/15) and 17.65% (6/34) respectively.

Cholangiocytes (biliary tree cells) but not hepatocytes (liver cells) express ACE2, supporting the notion of virus-induced liver damage via ACE2-expressing cholangiocytes. Gamma-glutamyl transferase, a diagnostic biomarker for cholangiocyte damage is an important prognostic indicator in patients with damage to the hepatobiliary system. Dysregulated immune status, cytokine storm and drug induced liver toxicity remain to be the most pertinent causes for multiorgan damage in a Covid patient. Meanwhile, presence of co morbidities in individuals only contributes to the susceptibility and severity of response to the virus. (Oyelade *et al.*, 2020; Wang *et al.*, 2020)

Taken together, the alterations in ACE2 receptor expression (upregulation) in CKD patients supplemented by alteration in kidney function characterized by increased serum creatinine and urea nitrogen, may explain the observed kidney dysfunction in Covid-19 and explain the increased susceptibility of CKD patients to Covid infection. (Oyelade *et al.*, 2020)

**Challenges for India – Combating Covid and Diabetes**

India is one of the worst hit countries with the highest disease burden globally to be hit by the effects of the pandemic owing to its high population density, inadequate health infrastructure and high prevalence of co morbidities like diabetes and hypertension. Despite timely declaration of a Pan India Lockdown and efforts to create awareness about social distancing in the post lockdown phase, the number of infected patients only seems to increase rampantly. Poor healthcare infrastructure weakens the response to epidemiological outbreak due to paucity of testing services, weak surveillance system, shortages and above all poor medical care. Rural India which contributes over 50 percent of the population composition is the worst affected sphere and is being looked upon as a potential Covid reservoir or hotspot in the coming months. Apart from the economic suffering, rural Indian population is bound to suffer the most in terms of access to healthcare services. The pandemic poses a unique opportunity to India to combat its poor health infrastructure sector and overcome shortcomings (Kumar *et.al.*, 2020).

The disease burden of diabetic population is high in India and contributes significantly to higher infectivity and mortality rates seen in Covid patients. A study was conducted on Covid-19 patients (n=22) with diabetes to evaluate the biochemical parameters during the course of infection. It was observed that levels of serum interleukin-6, total leukocyte count, D- dimer, fibrin degradation products (FDP) and neutrophil-lymphocyte ratio were much elevated as compared to control group (n=58). Also, the blood glucose levels of diabetic group were extremely poor as HbA1c levels was more than 8 gm% as compared to control group. It can be concluded that diabetic patients suffering from Covid-19 infection required much frequent administration of insulin therapy to manage the elevated levels of blood glucose (Bhandari *et al.*, 2020).

**Vaccine Development and Clinical Trials**

Almost a year after the emergence of the novel strain of corona virus, vaccinations against the same are being rolled out for emergency use. Biopharmaceutical companies in collaboration with researchers namely Pfizer-BionTech, Moderna in the US and Oxford-Astrazeneca in the UK got approval for mass vaccine production. Vaccines were being administered in massive drives in countries such as Britain, Canada, Bahrain, United States, India, China, Mexico, Malaysia, Switzerland and many other countries. Adverse drug reactions and ill effects of the vaccine after rigorous clinical phase trials and administration in mass population were tolerable. Covaxin, India's first indigenous vaccine was developed by Bharat Biotech International Limited along with Indian Council of Medical Research and National Institute of Virology, Pune. Serum Institute, Pune in collaboration with Oxford University and AstraZeneca became a forerunner in the vaccine race and helped millions in

getting vaccinated.

**Conclusion**

This systematic review suggests that people with any co-morbidity are the most susceptible targets for the CoV-2 causing lethal infections like severe pneumonia or multiple organ failure eventually leading to deaths with highest rate of mortality. Hence it is suggested that legitimate care and treatment must be provided to this population in order to avoid any complications. Also, there is a need to innovate vaccine for immunoprophylaxis is imperative and is the need of the hour for densely populated countries like India. Indian pharmaceutical companies in collaboration with biotechnological labs seem to be taking the challenge to develop the vaccine against the novel corona virus and will be a promising market as well a mass producer of the vaccine in the future.

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