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# Analysing the Bidirectional Relation between Covid - 19 and Diabetes and the Potential Prognostic Factors and Comorbidities.

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*(review paper)*

***Abstract:*** *The COVID - 19 pandemic that originated in China has resulted in a lot of focus on diabetes patients because of the poor prognosis observed in Coronavirus disease patients who have diabetes. The worsened prognosis is believed to have a multifactorial basis and is caused by various comorbidities such as hypertension, cardiovascular disease, and obesity as well as other factors such as age, sex, and ethnicity. The purpose of this paper is to analyse of these factors and simultaneously provide insight into the role the coronavirus disease may play in the development of new onset diabetes or metabolic complications in pre-existing diabetes in individuals.*

***Keywords:*** *Coronavirus disease, comorbidities, new-onset diabetes*

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## I. Introduction

Coronavirus disease is an infectious disease caused by a recently discovered coronavirus. This is a family of viruses that causes respiratory and gastrointestinal disorders that get their name from the crown like protein structures on their surface. In the case of COVID - 19 the causative agent is the SARS - coV - 2 virus.

| | **Article type** | **Study population** | **Prevalence of diabetes** | **Outcome** | **Risk** |
|---|---|---|---|---|---|
| Kumar et al. | meta - analysis | 16003 | 9.8% | Severe disease | 2.09-3.62 |
| Zhang et al. | retrospective | 258 | 24% | Mortality | 1.37-2.64 |
| Barron et al. | Cohort study | 61414470 | 4.7% | Mortality | 1.97-2.09 |

**Figure 1 - COVID 19 outcomes according to pre-existing diabetes**

The clinical presentation of COVID 19 is a mild to moderate respiratory illness that most people recover from. However, in the case of senior citizens and people with underlying medical issues like diabetes, cardiovascular disorders, and cancer the likelihood of developing a serious illness is higher. Symptoms include fever, cough, shortness of breath, and body ache. It has been determined that the virus spreads primarily through infectious secretions like saliva and discharge from the nose while coughing or sneezing. There are currently no specific vaccines or treatments but there are several clinical trials underway to evaluate potential treatments.

The purpose of this article is to analyse the prevalence of worse prognosis of this viral infection among diabetes patients. According to the American Diabetes Association, the mortality rate among diabetes patients was 7.3% more than three times that of the overall population. A research published in the journal of the European Association for the Study of Diabetes by Professor Bertrand Cariou and Professor SamyHadjadj to specifically analyse the effect of COVID 19 in hospitalised patients with diabetes has found that 10%patients die within 7 days of hospital admission and 25% are intubated and mechanically ventilated by this point.

Diabetes is increasingly proving to be a risk factor for hospitalisation and mortality of the coronavirus disease. In a study of 52 intensive care patients diabetes was a comorbidity in 22% of the 32 non-survivors. In another study of 173 patients, 16.2% had diabetes. When intensive and non-intensive care patients were compared, a two fold increase in the incidence of patients with diabetes was observed in intensive care.

Even in previous cases of disease epidemics infection rates were observed to be particularly higher in patients with diabetes. It has been generally seen that diabetes does not necessarily increase the risk for COVID 19 viral infection but rather severe coronavirus disease is more frequently observed in patients with diabetes.

A retrospective study carried out in china observed that diabetes patients with COVID 19 experienced severe pneumonia, higher concentration of lactate dehydrogenase, alpha hydroxybutyrate, and alanine aminotransferase, and had fewer lymphocytes with high neutrophil count. This study compared a group of 24 patients with diabetes to a group of 26 patients without diabetes and a 16.5% higher mortality was observed in the former.

A survey of 23,804 hospitalised patients with severe COVID 19 conducted in England showed that 32% had type 2 diabetes and it increased the probability of death by 2.03 times.

## II. Possible Prognostic Factors

*(A) HYPERTENSION*

It is uncertain whether hypertension is a risk factor for acquiring COVID 19. It is a common feature of type 2 diabetes and a comorbidity often seen in patients of the coronavirus disease. Several organisations have addressed the issue of blood pressure control in the context of reducing disease burden regardless of the direct impact on infection susceptibility. Hypertension is often observed in COVID 19 patients and is believed to play a role in the clinical characteristics of the disease.

Hypertension patients are frequently treated with Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARBs). The SARS coV 2 virus binds to the ACE2 to enter the lungs and target other body organs. ACE inhibitors and ARBs play a role in increasing the level of ACE2 and this could lead to a rise in the binding of the virus. Theoretically, this would imply an increase in the pathophysiological impacts of the viral infection. Experimental data, however, indicates that ACE2 protects the lung from injury. It essentially functions by forming angiotensin 1 - 7 from angiotensin (ii) and reduces the inflammatory impact of angiotensin (ii). This reduction in inflammation could help prevent the development of acute respiratory distress syndrome, myocarditis, and acute kidney injury which is often observed in coronavirus patients. ARBs have been recommended as a potential avenue for treatment as they would function to increase the circulating ACE2 which would bind to the virus and diminish its capacity to injure the lungs. This has not yet been demonstrated in patients.

Therefore, we still need conclusive evidence to prove the impact, whether positive or negative, of hypertension, ACE inhibitors, and ARBs on the outcomes of COVID 19

| | **Total (*n* = 225)** | **Non Hypertension (*n* = 160)** | **Hypertension (*n* = 65)** | ***P* value** |
|---|---|---|---|---|
| Fever | 190 (84.4%) | 136 (85%) | 54 (83.1%) | 0.718 |
| Cough | 143 (63.6%) | 108 (67.5%) | 35 (53.8%) | 0.054 |
| Dyspnea | 113 (50.2%) | 76 (47.5%) | 37 (56.9%) | 0.200 |
| Expectoration | 39 (17.3%) | 32 (20.0%) | 7 (10.8%) | 0.097 |
| Muscle ache | 19 (8.4%) | 12 (7.5%) | 7 (10.8%) | 0.424 |
| Diarrhea | 24 (10.7%) | 13 (8.1%) | 11 (16.9%) | 0.053 |
| Headache | 2 (0.9%) | 1 (0.6%) | 1 (1.5%) | 0.495 |
| ICU admission | 32 (14.2%) | 18 (11.3%) | 14 (21.5%) | 0.045 |
| Death | 37 (16.4%) | 23 (14.4%) | 14 (21.5%) | 0.189 |

**Figure 2 - clinical characteristics of hyper-intensive and non-hyperintensive COVID -19 patients without other comorbidities**

*(B) CARDIOVASCULAR DISEASE*

An analysis of the cases reported to China's Infectious Disease Information System found that the mortality of patients with cardiovascular disorders could be upto 10.5%. It was also found that CVD was a more powerful prognostic determinant than a history of smoking and chronic pulmonary disease despite the fact that coronavirus disease is considered primarily respiratory disease.

Patients with cardiovascular disorders display worse clinical outcomes and several CVD risk factors are known to impact the prognosis of covid patients but they have not been linked to increasing the likelihood of developing the infection.

Acute myocardial injury is a common cardiovascular complication associated with COVID 19. This is indicated by elevated levels of high sensitivity cardiac troponin I above the 99th percentile upper reference limit. Approximately 8-12% of the coronavirus positive cases have developed significant cTnI elevation. An autopsy study of patients who died due to SARS during the Toronto SARS outbreak, showed viral ribonucleic acid in 35% of the human hearts, providing evidence to prove direct myocardial injury by the virus.

| | Myocardial Injury | Underlying CVD* | Mortality* |
|---|---|---|---|
| **Shi et al.[3] (N=416)** | 19.7% | CHD: 29.3% vs 6.0%<br>HF: 14.6% vs 1.5% | 51.2% vs 4.5% |
| **Guo et al.[14] (N=187)** | 27.8% | CHD: 32.7% vs 3.0% | 59.6% vs 8.9% |
| **Han et al.[13] (N=273)** | 9.9% | - | 22.8% vs 5.1% |
| **Zhou et al.[1] (N=145)** | 17% | - | OR: 80.1 |

**Figure 3 - mortality associated with COVID - 19 and its relation with myocardial injury.**

Both Tachy- and Brady- arrhythmias are known to occur in the coronavirus disease. A study describing clinical outcomes in 138 Chinese patients showed 16.7% occurrence of arrhythmia and this was higher in ICU admitted patients (44%) in contrast to those who did not require ICU admission.

*(C) OBESITY*

Obesity can cause more severe symptoms in COVID 19 patients and can significantly worsen prognosis. Obese patients, measured using body mass index, can experience difficulty in getting intubated and obtaining diagnostic imaging since these machines generally have a weight limit. Obesity can also cause immune system disruption through processes like cytokine production, altered monocyte, and lymphocyte function, natural killer cell malfunction, and diminished dendritic cell function along with a reduced response to antigen stimulation. Obesity is essentially pro-inflammatory and also induces oxidant stress to adversely affect cardiovascular function.

Moreover, obesity can be directly linked to other comorbidities like atherosclerosis, coronary artery disease, cerebrovascular strokes, and osteoarthritis which increase susceptibility to COVID 19. Obesity can also serve to restrict ventilation by disrupting diaphragm excursion.

Another significant implication of the correlation between obesity and coronavirus disease is the shift it may cause in terms of younger people suffering from the infection. Studies indicate and inverse relation between age and BMI, in that younger individuals admitted to hospitals are more likely to be obese.

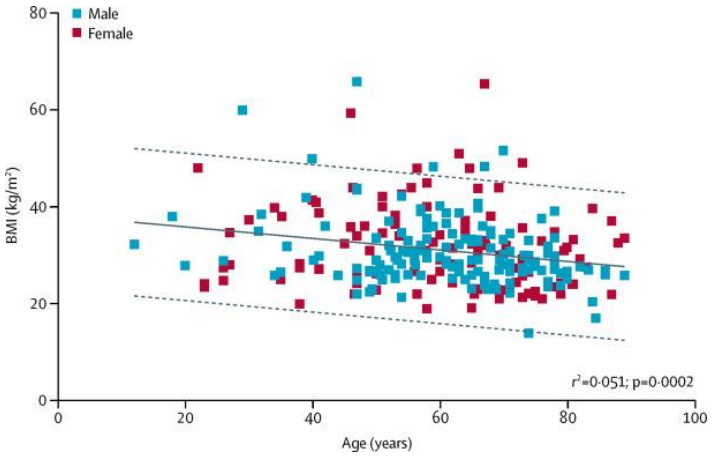


**Figure 4:Negative correlation between BMI and age in 265 patients with coronavirus disease 2019 in intensive care units in the USA. BMI=body-mass index. The solid line is the least squares linear regression model fit. Dashed lines are 95% prediction bands.**

## III. Impact Of COVID - 19 On Diabetes

We have looked at how diabetes increases the potential for the development of severe coronavirus disease. Patients with diabetes have a greater prevalence of comorbidities such as hypertension (56.9%), cardiovascular disease (20.9%), and cerebrovascular disease (7.8%) than those without diabetes (28.8%, 11.1%, and 1.3% respectively).

At the same time, it is also important to look at the mechanism with which COVID - 19 can lead to new-onset diabetes and also metabolic complications associated with pre-existing diabetes.

The SARS-coV-2 virus binds to ACE2 and this may result in alterations in glucose metabolism furthering diabetes complications. ACE2 is known to be expressed in important organs associated with metabolism like pancreatic beta cells and kidneys.

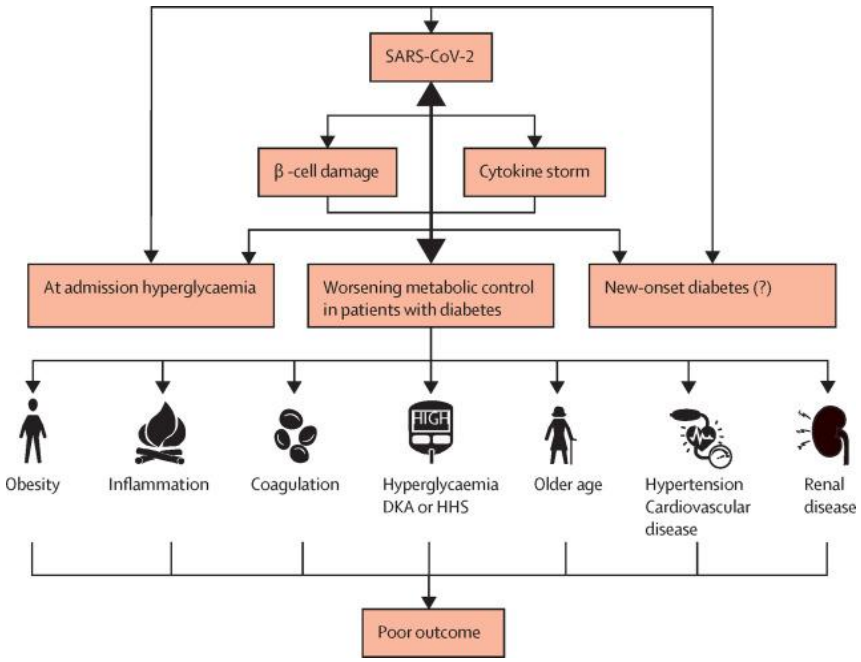


**Figure 5: bidirectional relation between COVID - 19 and diabetes**

There is considerable evidence for the potential diabetogenic effect of COVID - 19. However, there are several questions that continue to persist. Are the changes in glucose metabolism permanent or transient? Is it typically type 1 or type 2 diabetes mellitus or does new onset diabetes include a new sub-stratified type of the disease? Do patients remain at higher risk for diabetic ketoacidosis and other diabetes associated complications even after the infection is resolved?

Hopefully further research will help us answer many of these questions.

## IV. Conclusion

Diabetes management in coronavirus disease patients presents physicians with a great clinical challenge as it increases the likelihood of a worsened prognosis and even mortality. Diabetes is a fairly common disease, especially in India. As such, it brings forth a large segment of individuals with increased susceptibility to severe COVID 19. Moreover, increasing metabolic complications in cases of pre-existing diabetes as well as new onset diabetes induced due to the coronavirus is concerning. Physicians have to balance glucose-lowering treatments with virus specific treatments which can prove to be challenging. An integrated team approach and careful assessment of the multifactorial basis of poor prognosis of COVID - 19 in diabetes patients is extremely crucial.

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