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PREDICTING MORTALITY OF COVID PATIENTS WITH COMORBIDITIES

(Review Article)

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Abstract

Covid-19, an ongoing pandemic, is an emerging ground with several published studies. In general, Covid-19 infections occurring in pre-existing comorbidities stand with the greatest risk of mortality. Importantly, Age is a significant unmodifiable factor that further worsens outcomes. This paper aims to propose a prediction score for the mortality risk of Covid-19 in certain chronic conditions.

Introduction

In December 2019, in Wuhan, China, Covid-19 infections emerged as unknown pneumonia [97]. The virus's ability to spread through air droplets and a higher infectivity rate soon unfolded it into a threatening pandemic. By February 1st 2021, according to the WHO, the confirmed cases stand at around one hundred million and has claimed more than two million lives [40]. The most common comorbidities that increase the adverse outcomes are hypertension, diabetes and obesity [69]. Despite that, elderly individuals face a high risk for severe Covid-19 infection since Age-related physiological and immunological changes worsen the outcome [60]. Moreover, Age is a crucial undeniable risk factor.

This paper aims to review specific comorbidities and establish a sample scoring system for the mortality rate associated with Age and chronic conditions in Covid-19.

Cardiovascular and hypertension in covid-19 patients

Hypertension and cardiovascular diseases are among the leading comorbidities found in COVID-19 patients. To give an illustration, a nationwide study in Wuhan, China, shows Hypertension and Cardiovascular conditions' prevalence as the first and third common diseases among individuals infected with Covid-19 [31]. Based on few studies, that localized ACE2 receptor [26,75], It is evident that a vast majority of expression appears in type II pneumocytes, cardiac myocytes, GI tract, and blood vessel cells, which potentially explains the predilection of COVID-19 in the lung and cardiovascular system.

Furthermore, coexisting chronic conditions in infections are apparent to persuade worse outcomes. A study conducted in Wuhan [98] depicts the common concurrent comorbidities being hypertension (38.75%) and coronary artery disease (11.3%) in Covid-19. Despite that, the risk of mortality and adverse outcomes in concurrent diseases are still uncertain. Therefore, these vulnerable patient groups need targeted treatment and preventative strategies urgently.

Cardiovascular Disease

Cardiovascular diseases (CVD) are the number one leading cause of death globally. Nevertheless, little is known about the prognosis of CVD patients in Covid 19 infection. The study conducted on the association of CVD and non-CVD patient's prognosis in COVID-19 [55], illustrates that cardiovascular conditions potentially lead to poor outcomes in COVID-19 infection.

Mortality risk in CVD and the course of the disease can be predicted through biomarkers. Affirmatively, a study conducted in Italy [86], with 397 patients, demonstrates the elevation of biomarkers and its associated mortality. Moreover, the study based in China exemplifies that 12% of patients infected with Covid-19 experience myocardial injury [97]. Conclusively, COVID-19 infection causing elevation of cardiac markers such as troponin T and CK MB during cardiac manifestations might be justified.

The cardiac manifestations of COVID-19 can potentially be explained by the below mechanisms:

1. Myocardial damage through activation of inflammatory cytokine release

SARS 2 (COVID-19) is proposed to enter through the ACE2 receptor and causes modification of signalling response. Therefore causes increased release of cytokines and disproportionate inflammatory activation [98,53]

2. Plaque rupture

Viral infections causing inflammation and increased endothelial shear stress destabilizes plaques leading to worse complications such as acute myocardial infarction.

3. Electrolyte imbalance

Electrolyte imbalances are determined to be caused by two main reasons:

- In general, severe inflammatory reactions are self-sufficient to cause electrolyte imbalance.
- Arrhythmias due to hypokalemia through renin-angiotensin-aldosterone system interaction [17].

Notably, any of the above mechanisms can cause acute heart failure while dealing with COVID-19 patients. However, COVID -19 is a new research topic with growing information and new concepts and not definitive findings. We have data from previous viral infections and proven research studies that might relate to our ongoing pandemic.

Based on an analysis [97], 25 patients recovered from the SARS infection (2002 outbreak) after 12 years were considered. The results indicated the association between lipid metabolism disruption and corticosteroid therapy. Hence, cardiovascular patients treated with high doses of methylprednisolone should potentially need consideration for further evaluation in their later life. Importantly, drug usage in COVID-19 infections should be a meticulous process.

Side Effects of trial drugs used in treating COVID-19

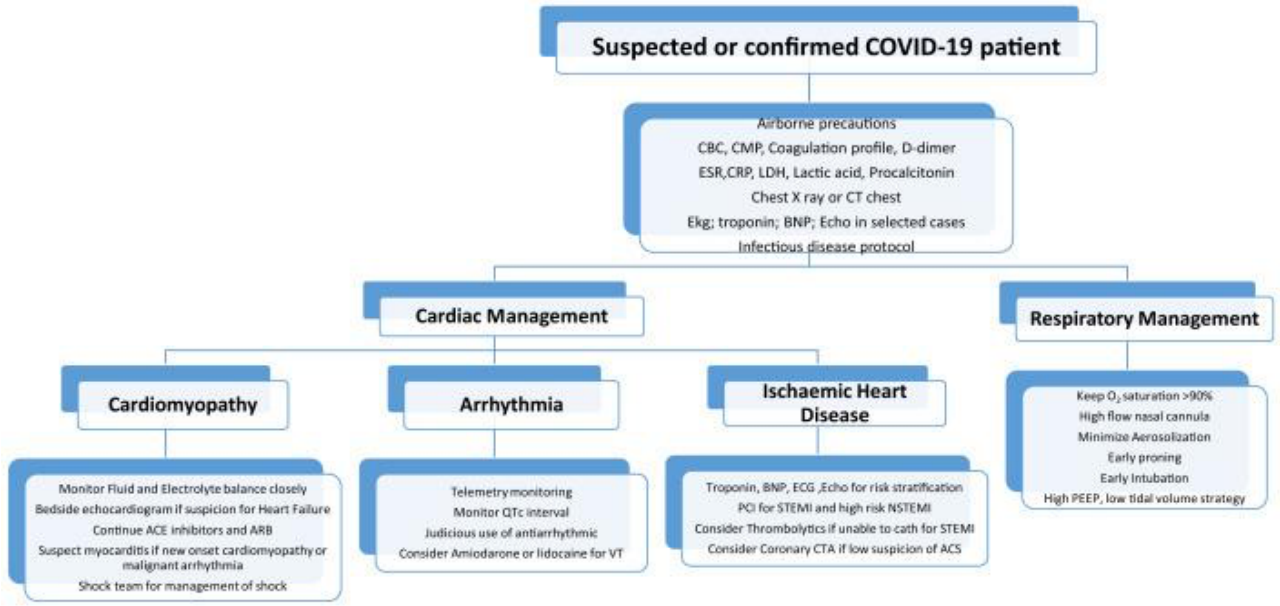
Hydroxychloroquine and chloroquine: Widely used antimalarial drugs such as hydroxychloroquine and chloroquine pose a risk of QT prolongation and Torsades de pointes [29,85]. Hydroxychloroquine could increase beta-blocker bioavailability and should be used cautiously.

Antiviral drugs: Lopinavir/ritonavir used as a treatment can potentially cause QT prolongation and potentially cause arrhythmias [14]. Combination with other drugs with similar effects should be avoided.

A combination of drugs such as azithromycin with hydroxychloroquine and or azithromycin with antiviral medication might be detrimental, since azithromycin causes QT prolongation as listed in source – FAERS (FDA Adverse Event Reporting System).

The management plan for pre-existing cardiovascular patients during COVID-19 infection is under evaluation. **Figure 1**. Depicts the proposed treatment algorithm [19].

Figure 1. COVID-19 treatment algorithm[19].



Abbreviations: CBC, complete blood count; CMP, complete metabolic profile; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; LDH, lactate dehydrogenase; CT, computed tomography; EKG (also ECG), electrocardiograph; BNP, NTpBNP, N terminal pro brain natriuretic peptide; Echo, echocardiograph; VT, ventricular tachycardia; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; CTA; computed tomography angiography; ACS, acute coronary syndrome.

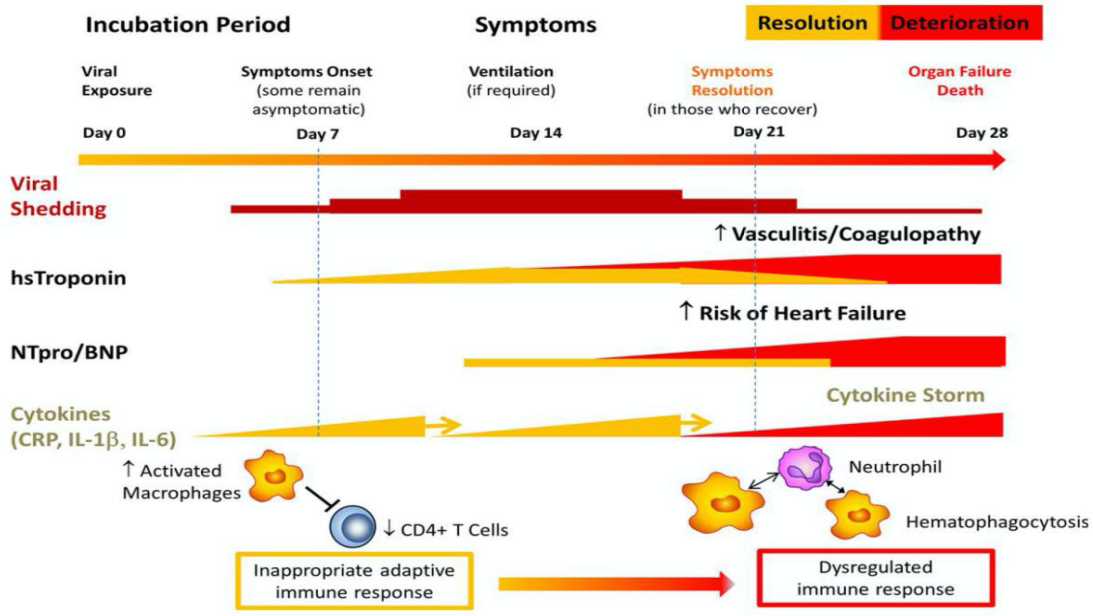
Biomarkers such as Troponin T, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and brain natriuretic peptide BNP can help diagnose cardiac complications. N-terminal proBNP elevation can help us determine cardiac wall stretching [73]. Elevated biomarkers do not always relate to cardiovascular complications but support the cardiovascular system's involvement and support the clinical diagnosis. **Figure 2**. Biomarkers in COVID-19 [57].

Moreover, Troponin T is mainly being considered as an essential biomarker since it indicates direct myocyte damage.

Troponin T

- Potentially could be used in intensive care units (ICU) to support clinical judgement [36].
- Elevation in cardiac events. TnT, based on a study [93], signifies the elevation in myocardial injury.
- By contrast, Troponin might be an independent risk factor for mortality, as illustrated in a study, conducted at Mayo clinic [6].

Figure 2: Biomarkers in COVID-19[21]



The mortality rate in cardiovascular

With this in mind, a study [33] consisting of 187 individuals had a mortality of 43; among them, patients with comorbid CVD with elevated TnT had the highest mortality rate of 69.4% and elevated TnT but without CVD was 37.5%, indicating cardiac injury being the predominant cause of fatality. Pre-existing cardiovascular conditions intuitively might weaken the body's reserve to fight the occurring disease. The data to predict the mortality rate and analyze the exact mechanism leading to adverse events such as myocardial infarction and myocarditis is far from definitive. Patients with cardiovascular conditions might need aggressive therapy and careful monitoring during the disease.

Hypertension

Hypertension, a medical condition that elevates blood pressure, significantly increases the risks of heart, brain, kidney, and other diseases. Neither uncontrolled blood pressure being a risk factor nor controlled individuals having reduced risk in Covid-19 are unclear. Nevertheless, hypertension is a pivotal chronic condition to research further. Recent studies on Angiotensin-converting enzyme inhibitor (ACE inhibitor) and Angiotensin receptor blocker (ARBs) drug usage in hypertensive patients are arguable.

Renin-angiotensin-aldosterone system and ACE inhibitor/ARB's usage in Hypertension

Studies propose SARS-CoV-2-S(COVID-19) has 80% similarity in spike protein as SARS COV1[38], and speculated to enter through ACE2 receptors [103] during the early phase. The anticipated outcome of severe COVID -19 infections through the usage of antihypertensive drugs are under investigation. ACE inhibitors and ARBs may potentially cause an upregulation of ACE 2 receptors [47]. Chronic usage might increase the viral entry and thus produce a severe infection. That said, these mechanisms are still theoretical from animal studies and not validated in humans. In view of above

findings, switching drugs in hypertension may result in effective reduction of viral entry in the near future.

On the other hand, a pathway called ACE-2-Ang-(1–7)-Mas axis counteracts the inflammatory reaction and possibly reduces the detrimental effect [80]. This proposed mechanism is due to the long term administration of the above-said drugs as well. Nonetheless, A study based in Wuhan Central hospital, consisting of 1178 patients, has provided no association between usage of ARB/ACE inhibitors and severity in hypertensive patients [54].

Theoretically, the discontinuation of ACE inhibitor /ARB's drugs might decrease the above said ACE 2 upregulations. But an aftereffect might scale down the preferred ACE-2-Ang-(1–7)-Mas and the resulting anti-inflammatory pathway. Above all, discontinuing life-saving drugs, i.e., ACE inhibitors/ARBs in a vast majority of comorbidities, could be harmful. In summation, whether ARB/ACE inhibitor's usage aids the patient through anti-inflammatory properties through ACE-2-Ang-(1–7)-Mas or promotes upregulation of the ACE 2 receptors causing a severe infection is uncertain.

Moreover, RAAS activation causes vascular complications in many comorbid conditions such as hypertension and diabetes. Given that the most severe forms of COVID-19 infection have resulted in hypertensive patients, long standing RAAS activation potentially links to the pathogenesis of the COVID-19 virus.

Association of severity in Blood group

The relation between ABO blood groups and Hypertension's severity observed in a study [77], signifies that AB blood group (Non-O blood group) vs O group individuals are likely to be associated with:1) Elevated Pro-thrombotic value, 2) Increased rate of death, 3) Increased risk of cardiac injury.

As far as we know, hypertensive patients' deterioration rate is far more significant than other comorbidities, as illustrated in this research which contemplates using the Kaplan-Meier survival curve and insists on a mortality increase in Hypertension [22]. Moreover, several kinds of research indicate the harsh reality about Hypertension causing catastrophic outcomes.

Plasma(ogen)

The plasminogen is theorized one of the common risk factors to increase susceptibility in comorbid individuals [46]. The study illustrates the plasmin role, potentially causing enhanced virulence and infectivity.

Repurposable drugs

The primary objective currently should be to spotlight the management methods followed worldwide and to reduce mortality. Newer drug regimes through analysis are currently ongoing.

Based on previous reports, testing alternative drugs such as carvedilol [82] and verapamil [46] are promising. Carvedilol is illustrated to reduce ACE up-regulation [74], and thus used as a potential drug in Covid-19. Previous studies have suggested that it could potentially reduce inflammation in myocarditis induced by viral infections.

Drugs that are under investigation:

1) Canakinumab [16] - a monoclonal antibody that targets IL-1β explicitly. Thus, it might be beneficial to decrease Th1 mediated cascade.
2) Roflumilast [92] - PPE-4 inhibitor. Proven effective in COPD patients.
3) Drugs targeting Spike protein.

Diabetes and obesity

The prevalence of Diabetes and Obesity in the world make these crucial comorbidities when approaching patient care in the COVID-19 pandemic. Knowing what burden these diseases bring and how they influence a patient's prognosis and overall health can be enlightening. With enough serious research, structuring an integrated, unique prediction medium is not without benefits. Though they are often hand in hand, our review will include the individual factors of Diabetes and Obesity in light of a COVID-19 positive victim.

Diabetes

Some might argue diabetes is a pandemic in and of itself in the world today. The past documentation of diabetic patients proves it has walked the earth with us for some time, though Diabetes Type 2 is more present now than ever. Due to the many stricken by this pathology, numerous studies and

treatment regimes have already been implemented with great success. Despite this, there is no cure to this modern ailment. Now enter SARS CoV-2, the new pandemic on block, and we might have to view diabetes in a new light.

COVID-19 goes with comorbidities like winter and the flu. Their combination in exacerbating a patient's condition and causing mortality belies the true meaning of the word synergy. In a study identifying the main proponents of associated comorbidities with COVID-19 cases, diabetes revealed itself to be a front contender, though the authors do admit the lack of concrete data prevents them from figuring out to what extent [88]. Other researchers propose that both were an 'unholy interaction of two pandemics' because of their effect on one another [64]. Diabetes increases the chance of and worsens the prognosis of a SARS CoV-2 infection. Likewise, the reaction to and treatment for coronavirus rapidly deteriorates the glucose control of a diabetic [15].

In order to understand how diabetes affects the prognosis and risk of morality in a COVID-19 patient, the pathophysiology as well as the mechanisms of each must be considered. At the same time, past outbreaks of similar microbes may also be referenced for more calculated conclusions.

In general, SARS CoV-2 enters the cell through surface S-glycoprotein attachment to host cell ACE-2. ACE-2 is expressed in many cells throughout the body, including type 1 and 2 alveolar epithelial cells in the respiratory system [81]. Cells expressing the same entry point include pancreas, intestinal epithelium, rental tubular epithelium, cardiac cells and vascular endothelium.

Once entry has been achieved, inflammatory responses recruit T helper cells and other inflammatory cells. This causes a cytokine storm leading to multi-organ dysfunction and failure. Assuming the patient has no other conditions that can contribute or negate, this is the usual course of the infection.

Now add in diabetes. So far, the research that is out there found that the increased risk and severity of SARS CoV-2 seen in diabetic patients can be attributed to:

1. ***Increased ACE-2 Expression***
   - One study identified increased expression of ACE-2 in renal, liver and pancreas [71].
   - Diabetic patients expressing more ACE-2 might be predisposed to SARS CoV-2.
2. ***Increased Furin***
   - Though ACE-2 is the entry receptor for SARS-2 CoV-2, a pro-protein membrane-bound protease contributes to coronavirus entry into the cell.
   - Diabetics have been found to have more furin [24].
3. ***Impaired immune functionality***
   - Past studies from the MERS-CoV show that diabetic mice experienced a delay in inflammation and immune response.
   - Likewise, decreased amounts of lymphocytes were seen in COVID-19 patients [51].
4. ***Increases in Interleukin-6 (IL-6)***
   - IL-6 is found to be increased in COVID-19 infection as well as in non-COVID-19 patients diagnosed with diabetes.
   - Synergistic effect upon prognosis is a possible method of severity [58].
5. ***SARS infection causing hyperglycemia***
   - In a 2010 study, patients with SARS infection were seen to have hyperglycemia with no history of diabetes.
   - Further investigation revealed that SARS could bind to pancreatic islet cells, damage them and cause an acute diabetes [101].
6. ***Anti-diabetic drugs***
   - Thiazolidinediones (TZD) was seen to increase the risk of pneumonia [29].
   - Pioglitazone [102] and liraglutide [71] were found to increase ACE-2 expression.
   - DPP4 inhibitors have been associated with increased risk of upper respiratory infection, but more data is needed to correlate that risk with COVID-19 and diabetes outcomes [43].
   - Similarly, in cases of diabetic nephropathy or macrovascular disease, ACE/ARBs, statins, calcium channel blockers and aspirin require more evidence before contraindications can be prescribed [81]

Though there is still more to be discovered, these factors influence the outlook of SARS CoV-2 infection in diabetes. This is of course not including the various acute and chronic complications faced in diabetes, each of which could add exponential risk upon the patient depending on how well controlled their diabetes is found to be. Those with progressive, uncontrolled diabetes have higher incidences of HTN, cardiovascular disease and the like. At the same time, having only diabetes with COVID-19 by no means reduces from any potential risk of adverse events. In fact, a study found COVID-19 patients, without any other comorbidity other than diabetes, to be at increased risk of a myriad of critical complications [34] including:

1. Severe pneumonia and ARDS
2. Release of enzymes related to tissue injury
3. Uncontrolled and excessive inflammation responses (due to increases of inflammatory-related biomarkers),
4. Increased hypercoagulable state
5. Dysregulation of glucose metabolism
6. Greater need of tracheal intubation
7. Associated death within 7 days

Yes, these complications look dire and it is exactly why diabetes increases the death rate in COVID-19 patients [1]. Taking it further, what's interesting is these mechanisms and complications are surprisingly similar to the findings of past viral infections. If we compare past data, this allows us to gather further insight into the true risk of diabetes amidst infectious pathologies:

1. Diabetes and associated plasma glucose levels were an independent risk factors in 2002-2003 outbreak of Severe Acute Respiratory Syndrome (SARS-CoV-1) [100].
2. 'Diabetes increased likelihood of medical consultation and risk of death due to influenza' according to researchers studying the Influenza A outbreak of 2009 [3].
3. Patients with underlying diabetes were associated with life-threatening severity and a 35% mortality in the sudden appearance of 2012's Middle East respiratory syndrome coronavirus (MERS-CoV) [7].

As past studies of similar outbreaks (e.g., SARS [100]and H1N1[8]) show, glycemic control could be a predictor of a patient's course and status in regards to COVID-19. This can prove to be arduous as blood glucose readings usually require a bedside manner differentiated from current regulations of lockdowns and social distancing. Those not critically ill may circumvent this obstacle with self-testing and telecommunication with their care provider, but not all have this luxury. The prospect increases if the patient is elderly, lives alone and suffering from physical, mental or emotional afflictions. What's worse, the acute complications of diabetes (namely DKA and HHNS) are both precipitated by stress and improper insulin management. Inadvertent or forgetful management of medication concurrent with an exposure to coronavirus could be the perfect storm that deteriorates a diabetic patient's health before word gets out. All and all, diabetic patients are facing an all too different face of the COVID-19 pandemic. Quantifying the risks and mortality for patients could arm medical providers with a realistic and sure approach to preserve the lives of those in their care.

Obesity

Obesity, or excess of adipose tissue due to imbalance of food intake and energy expenditure, is also a factor that can't be ignored and is very similar to diabetes. What's worse, both are seen in old and younger generations thanks to the rising tide of adolescent obesity [63]. The wide prevalence throughout the world has been partly attributed to the nutrient values of everyday diets, those high in saturated fats, sugars and refined carbohydrates [11]. These more available, yet unhealthy foods leave many at risk of the current COVID-19 pandemic situation. In fact, obesity was found in a New York study to be one of the leading clinical features amongst 4,103 patients being treated for COVI-19 [68]. Furthermore, a separate study conducted with 1,317 diabetic participants hospitalized for COIVD-19 in France associated the link of obesity with severe outcomes. Patients who required mechanical ventilation via tracheal intubation and/or experienced death within 7 days of admission were more positively associated with increased BMI rather than glucose control [15]. This leads us to believe that obesity, often analogous to diabetes, is in a

class all its own as seen in the high risk of mortality is associated with COVID-19 infection in patients with obesity [42].

Charting out the mechanisms of increased risk in obesity and COVID includes:

1. *Increase risk of other risk factors*
   - Increased fat mass was causally related to hypertension, diabetes mellitus, coronary artery disease, stroke, atrial fibrillation, renal disease, and heart failure [78].
2. *Impaired immune response*
   - Similar to diabetes, obese individuals have an altered immune function perhaps due to the metabolic and nutrient from insulin resistance and reduced beta-cell function [61].
   - SARS CoV-19 causes a 'cytokine storm', further weakening the immune system [50].
   - Fat depots have also been linked to disruption of immune cells, preventing interactions, survival and proliferation [84].
3. *Increase thrombotic complications and endothelium imbalance*
   - Amongst COVID-19 infections, risk of disseminated intravascular coagulation and venous thrombosis have been associated [91].
4. *Decreased respiratory performance*
   - Decreased lungs volumes (forced expiratory, forced vital capacity, etc) hamper the recovery period of obese individuals [78]
   - Furthermore, obesity decreases lung compliance and hinders normal diaphragm movement [20].
5. *Increased inflammatory status*
   - Like diabetes, interleukin-6 and C-reactive protein levels are increased.
   - This could be on account of adipose tissue being highly inflammatory, with increased expression of cytokines (eg, TNF-alpha, IL-1, adipokin) [87].
   - Increased oxidative stress is also a contributing factor [12].
6. *Difficulty in receiving healthcare*
   - Medical providers often aren't able to properly perform examinations and treatments for obese patients, such as performing imaging and overall handling [24].
7. *ACE-2 expression in adipose tissue*
   - Adipose tissue is generally found to have more ACE-2; its accentuated presence in obesity allows further ease of of SARS CoV-2 infection [76].

Smoking and Respiratory Comorbidities:

As COVID-19 is a respiratory disease by itself, Smoking and COPD play a role in the prognosis of affected patients. Smoking cannot be called comorbidity but is the primary cause of an array of respiratory conditions, including COPD. So we have to look into smoking as a separate condition rather than a cause of several respiratory problems. Respiratory Failure is the primary cause of death in patients affected with SARS-CoV-2, patients with preexisting respiratory problems, such as COPD, have a higher risk of mortality. Our review will attempt to explain the effect of these conditions in a patient affected with COVID- 19.

Smoking

There are more than 1.2 billion smokers worldwide [95]. Though smoking is not a comorbidity, it is the primary cause of a variety of lung problems. So therein lies the novelty to explore this topic further. ACE 2 is the receptor used by SARS-CoV-2 to enter the host cell [38]. A study conducted by Leung et al. [52] revealed that there is a higher expression of protein ACE 2 in the small airway epithelia of smokers than in nonsmokers. They concluded that this might predispose smokers to an increased risk of COVID-19 infection. But a review study conducted by Marco et al. [72] says that current smoking is not a risk factor for neither acquisition nor severity of COVID-19. Two other studies [32,56] support the conclusion of the study by Marco et al. [72]. Thus, it is safe to assume current smoking may not be a problem, but that does not mean smokers are not at risk.

Since the primary cause of death in COVID-19 is respiratory failure, smoking is the most common cause of lung damage. An array of lung problems have their effect on the prognosis of COVID-19 infection.

Since the damage accumulates over a long period, it is almost certain that smokers who have smoked for a long time have an increased risk of progression if they get infected by SARS-CoV-2. A meta-analysis conducted by Patanavich R and Glantz A [66] supports this theory by concluding that "smoking is a risk factor for the progression of COVID-19, with smokers having higher odds of COVID progression than never smokers". To conclude, we can say that current smoking does not increase the rate of mortality, but the damage of lungs and increased ACE 2 expression due to smoking puts patients at a higher risk of progression of COVID- 19 infection. Thus it becomes a high risk when the patient has a history of smoking.

Respiratory Comorbidities

COVID-19 is a respiratory infection, which causes a great deal of damage to the lungs. If a patient already has damaged lungs, it makes the prognosis of COVID-19 even worse. There are a lot of conditions that can damage the lungs. Two of them are COPD, and Asthma. In this review, we will look into these specific conditions as comorbidities.

COPD

SARS-CoV-2 is transmitted mainly by respiratory droplets. The virus uses ACE 2 protein in the respiratory epithelium as the entry point. A study [52] shows there is more ACE 2 gene expression in patients with COPD than patients without COPD. Cai et al. [13] found out that there is increased ACE 2 gene expression in COPD patients to smokers. Another study by Smith et al. [83] concluded that ACE 2 expression was higher in the whole lung tissue of COPD patients. From these studies, we can infer that their COPD patients have increased ACE 2 expression, which is a receptor used by SARS-CoV-2 to enter the host cell.

All these studies focus on the relationship between SARS-CoV-2 and ACE 2 in COPD patients, but we should also consider that COPD patients are already predisposed to respiratory infections. This could be because of decreased type 1 interferon production [39] or immunosenescence because of increased exhausted T cells and reduced memory T cells [27,48]. When we put all this together, we can say the prognosis of COPD patients is worse than a previously healthy patient.

There is a report of endothelial cell dysfunction in COPD patients, which results in increased apoptotic endothelial cells [49]. Increased permeability of airway microvasculature is also related to airflow limitations in COPD patients [62]. These show that COPD patients are susceptible to vascular injury. There is an increased amount of circulating coagulation factors in COPD patients [41]. This amount further increases during exacerbations [90]. COVID-19 infection will be the cause of exacerbation here. These studies show COPD patients are prone to coagulopathies. It also explains why there is an increased occurrence of Pulmonary embolism in COPD patients [2]. Considering all these studies, we can say that COPD patients are at higher risk of mortality.

According to a few studies done in China and America [4,32,59], the prevalence of COVID-19 in COPD patients is around 2-3%. A meta-analysis of 11 case series [5, 32, 59, 67, 69,18, 89] by Andrew et al. [38] showed an 88% increase in the risk of ICU admission or death in COVID-19 patients with COPD. Moreover, it also showed a 45% higher chance of developing severe complications. We cannot take this data at face value because most patients in these studies with COPD were also of age greater than 60. Age is one of the non-modifiable risk factors and comorbidity for the prediction of the outcome in COVID-19 infected patients. An Italian study [9] reported that patients with COPD were at a higher risk of severe respiratory failure. A Spanish study [89] observed a 70% increase in the risk of death among COVID-19 infected patients with COPD. A cohort study by ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) [21] with a sample of over 20000 showed chronic pulmonary diseases are associated with increased risk of death.

Thus with compiled information, we can say that COPD increases the risk of mortality in patients with COVID-19. It is also crucial to note that many of these comorbidities can appear together in a single patient. Though COPD may not increase the rate of mortality as much as hypertension or obesity, it plays a role significant enough to notice.

Asthma

It is safe to say that COVID-19, unlike many other respiratory infections, did not affect patients with asthma to the same extent. A study by José et al. [44] with a sample size of over 70000 concluded that significantly fewer patients with asthma are affected by COVID-19 than other comorbidities. It also concluded that the use of Inhaled Corticosteroids (ICS) showed a safer profile, implying the protective effect of ICS against SARS-CoV-2 infection. ICS may prevent SARS-CoV-2 entry because it can downregulate ACE 2 [25,67]. In these studies, it is found that ACE 2 gene expression is lower in the sputum of COPD and Asthma patients using ICS.

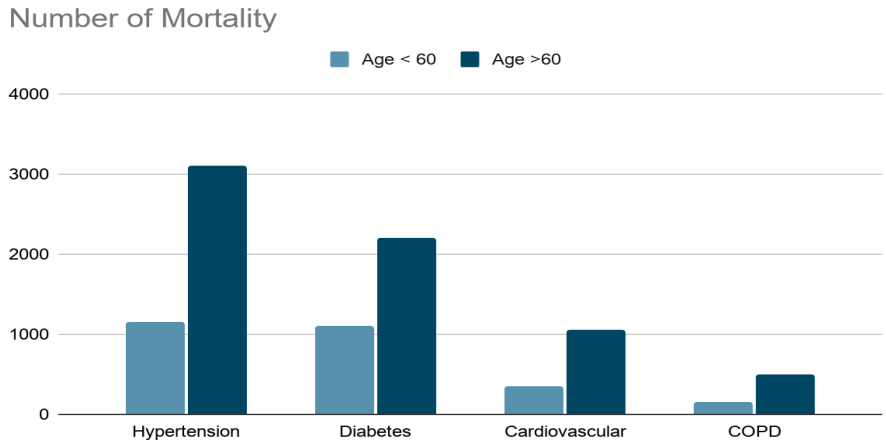
But a literature review by David et al. [35] concluded that there is no evidence of benefits or harms of ICS in COVID-19. An observational study from London [79] found increased mortality in COPD and Asthma patients using ICS. But a sensitivity analysis showed that the cause of mortality was simply due to the severity of the disease itself rather than ICS use. So the conclusion by David et al. [35] and José et al. [45] still stands correct. With this information, we can conclude that asthma will not play a significant role as comorbidity when predicting the mortality of COVID-19 infected patients.

Prediction of mortality

By understanding the interactions of the major comorbidities with COVID-19, we can appreciate how a predictive mortality score method would be beneficial to healthcare providers. Each patient presents a unique challenge and therefore requires a personalized approach. This, however, is difficult in a pandemic situation where clinicals and wards can be easily overwhelmed. By calculating the risk of mortality for patients with SARS-Covid infection, both triage and focused care can be acceptably achieved in any part of the world.

Generating a predictive mortality method still calls for applicable and accurate data to the geographical locations of patients. What comorbidity afflicting one nation will not always align with another nation's. A pertinent example can be seen in approaches by 2 different studies, one based in Wuhan, China[2] and another in Mexico [10]. Each had different statistics in terms of mortality/recovery rate, coexisting disorders and other differential data. But they were able to formulate predictive information to assist future, similar cases. We believe what they achieved was not only innovative and admirable, but also reproducible for all areas of the world.

As an example, we formed a similar approach using figures from West Bengal who diligently assemble and update their demographic data daily [95]. Due to lack of info we were unable to include Obesity and Smoking as fatal cofactors, though this doesn't eliminate their significance to a patient's prognosis. Below we surmised this data into a bar graph about mortality based on age, which statistically is already known to be the greatest modifier, and comorbidities.



Then we created a table for a predictive score report based on age range and applicable chronic disorders. A higher value proportionally infers that this patient is at a higher risk compared to others whose score is less.

Mortality Prediction Table (based on West Bengal data)	
Comorbidities	**Predictive Score**
Age >60	+2
Age <60	-2
HTN	4
Diabetes	3
Cardiac Disease	2
COPD	1
Mortality Predictive Score	
Low risk	0-3
Medium Risk	4-6
High Risk	7-9
Very High Risk	≥10

Conclusion

COVID-19 is a pandemic we can't ignore, especially when afflicting patients with compromising chronic illnesses. Cardiac Disease, HTN, Diabetes, Obesity, Respiratory Disease and Smoking are amongst the considerable coexisting conditions that threaten the prognosis of victims of SARS-CoV-2. We have included the pathways of how they interact with the virus and a solution of structuring a method of predicting mortality risk to give doctors a practical tool. This method was simulated from cited analyses conducted in Wuhan and Mexico respectively.

Unlike the many studies we cited in our investigation, our goal was to create a unique, world-wide predictive score report for determining mortality and adverse events in COVID-19 patients with comorbidities. Our research draws upon their contributions, of which we give them full credit and accolades. This study was compiled in an attempt to present a simple and universal tool for medical providers to apply in their own idiosyncratic situation. We understand that our own predictions are indeed fallible, due to inability to collect on-the-ground statistics as well as observing this data through the lens of ignorance. Despite that, we hope this score sheet allows healthcare experts with the means to make verdicts regarding the health of those in their care.

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