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Clinical Research

COMORBIDITIES IN COVID-19 AND ITS IMPACT ON PATIENT OUTCOME- A SYSTEMATIC REVIEW

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ABSTRACT In this article, we are reviewing the impact of comorbidities on patient outcome in COVID-19 infection. The data from this review shows that people already living with some co-morbidity are worse affected by COVID-19 than people without comorbidities. Also, older age-group patients have more signs and symptoms. This is majorly because of the weak immune system in older people having co-morbidities. Also, death rates among population with no preexisting comorbid condition is very less, i.e. 0.9 % only.

KEYWORDS : COVID-19, Comorbidities, Diabetes, SARS-CoV-2

INTRODUCTION:

An acute respiratory disease, caused by a novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV), the coronavirus disease 2019 (COVID-19) has spread throughout China and received worldwide attention. On 30 January 2020, World Health Organization (WHO) officially declared the COVID-19 epidemic as a public health emergency of international concern. The emergence of SARS-CoV-2, since the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, marked the third introduction of a highly pathogenic and large-scale epidemic coronavirus into the human population in the twenty-first century. As of 12th July 2020, a total of 12.9 million confirmed cases globally, with 8.54 lakhs confirmed cases in India and with 5.68 lakh deaths globally had been reported by WHO, mainly affecting the respiratory tract. Meanwhile, several independent research groups have identified that SARS-CoV-2 belongs to β-coronavirus, with highly identical genome to bat coronavirus, pointing to bat as the natural host. Importantly, increasing evidence showed sustained human-to-human transmission, along with many exported cases across the globe. The clinical symptoms of COVID-19 patients include fever, cough, fatigue and a small population of patients having symptoms of gastrointestinal infection. The elderly and people with underlying diseases are highly susceptible to COVID-19 infection and are prone to serious outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and cytokine storm.

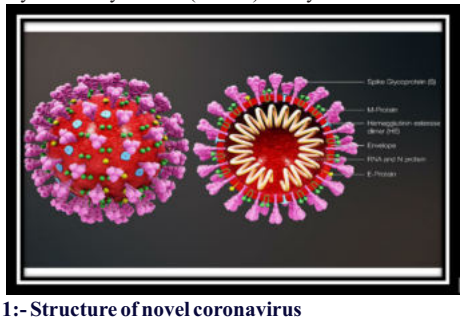
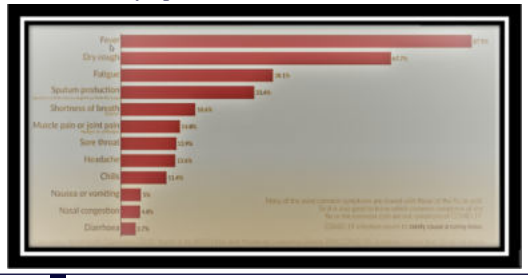


Figure 1:- Structure of novel coronavirus

Table 1:- Clinical symptoms of novel coronavirus



Genomics of coronavirus: Coronaviruses are enveloped viruses with a positive sense single-stranded RNA genome. [1] Four coronavirus genera (alpha, beta , gamma, delta) have been identified so far, with human coronaviruses (HCoVs) detected in the alpha-coronavirus (HCoV-229E and NL63) and beta- coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera. [2]

Virus genomic sequencing of five patients with pneumonia hospitalized from December 18 to December 29, 2019 revealed the presence of a previously unknown b-CoV strain in all of them. This isolated novel b-CoV shows 88% identity to the sequence of two bat-derived severe acute respiratory syndromes (SARS)-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21).

Pathogenesis of COVID-19:

Patients with COVID-19 show clinical manifestations including fever, non-productive cough, dyspnoea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia,[3] which are similar to the symptoms of SARS-CoV and MERS-CoV infections.[4]

Hence, although the pathogenesis of COVID-19 is poorly understood, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a lot of information about the pathogenesis of SARS-CoV-2 infection to facilitate our recognition of COVID-19. Coronavirus entry and replication of Coronavirus S-protein has been reported as a significant determinant of virus entry into host cells. [5] The enveloped spike glycoprotein binds to its cellular receptor, ACE-2 for SARS-CoV and SARS-CoV-2, [6,7] CD 209 L (a C-type lectin, also called L-SIGN) for SARS-CoV, DPP4 for MERS-CoV. The entry of SARS-CoV into cells was initially identified to be accomplished by direct membrane fusion between the virus and plasma membrane. It was then found that a critical proteolytic cleavage event occurred at SARS-CoV S-protein at position (S 20), which mediated the membrane fusion and viral infectivity. MERS-CoV also has evolved abnormal two-step furin activation for membrane fusion. Besides membrane fusion, the clathrin-dependent and -independent endocytosis mediated SARS-CoV entry is also implicated. [8,] After the virus enters the cells, the viral RNA genome is released into the cytoplasm and the viral genome begins to replicate. The newly formed enveloped glycoproteins are then inserted into the membrane of the endoplasmic reticulum or Golgi apparatus, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus.

Antigen presentation in coronavirus infection:

While the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC), which is a central part of the body's

anti-viral immunity. Antigenic peptides are presented by major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) and then recognized by virus-specific cytotoxic T lymphocytes (CTLs). Unfortunately, there is still lack of any report about it, and we can only get some information from previous researches on SARS-CoV and MERS-CoV. The antigen presentation of SARS-CoV mainly depends on MHC I molecules, [10] but MHC II also contributes to its presentation. In MERS-CoV infection, MHC II molecules are associated with the susceptibility to MERS-CoV infection. [11] Also, gene polymorphisms of MBL (mannose-binding lectin) which is associated with antigen presentation, are related to the risk of SARS-CoV infection. [12]

Humoral and cellular immunity:

Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. The antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG production. The SARS-specific IgM antibodies disappear at the end of 12 weeks, while the IgG antibody can last for a long time, which indicates that IgG antibody mainly plays a protective role. [13] Comparing to humoral responses, there are more researches on the cellular immunity of coronavirus.

In the acute phase, response in patients of SARS-CoV-2 is associated with a decrease in CD4þ and CD8þ T cells. Even if there is no antigen, CD4þ and CD8þ memory T cells can persist for four years in a part of SARS-CoV-2 recovered individuals and can perform T cell proliferation, DTH response and production of IFN-gamma. [14] Six years after SARS-CoV infection, specific T-cell memory responses to the SARS-CoV S peptide library could still be identified in 14 of 23 recovered SARS patients. [15] The specific CD8þ T cells also show a similar effect on MERS-CoV clearance in mice.

Cytokine storm in COVID-19:

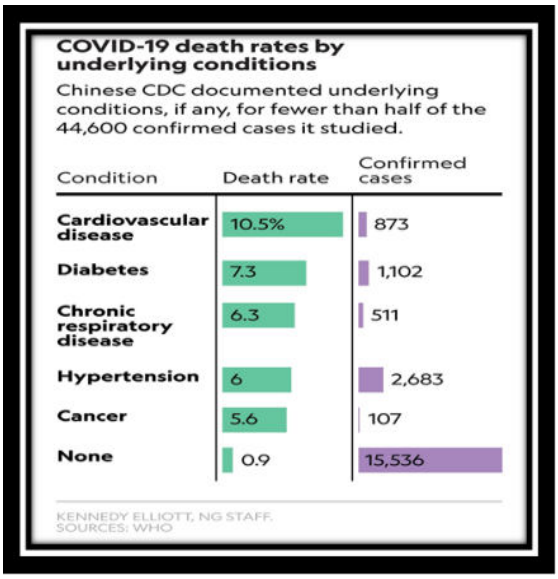
The report in Lancet shows ARDS is the main death cause of COVID-19. Of the 41 SARS-CoV-2-infected patients admitted in the early stages of the outbreak, six died from ARDS. [] ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-coinfections. [16] One of the main mechanism for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection. Similar to those with SARS-CoV, individuals with severe MERS-CoV infection show elevated levels of IL-6, IFN-a, and CCL5, CXCL8, CXCL-10 in serum compared to those with mild to moderate disease. [17] The cytokine storm will trigger a violent attack by the immune system in the body, causing ARDS and multiple organ failure, and finally leading to death in severe cases of SARS-CoV-2 infection, just like what occurs in SARS-CoV and MERS-CoV infection. [16]

Coronavirus immune evasion:

To better survive in host cells, SARS-CoV and MERS-CoV use multiple strategies to avoid immune responses. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs). However, SARS-CoV and MERS-CoV can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their dsRNA.[18] The antigen presentation can also be affected by the coronavirus. For example, gene expression related to antigen presentation is down-regulated after MERS-Cov infection.[19] Therefore, destroying the immune evasion of SARS-CoV-2 is imperative in treatment and specific drug development.

After the virus enters the cells, the viral RNA genome is released into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate. The newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus.

Table 2:- COVID-19 death rates in different comorbidities



Cardiovascular diseases and COVID-19

About 15% to 30% of the COVID‑19 patients are with hypertension and around 2.5% to 15% are with coronary heart disease. [20, 21,22]

Interestingly, several studies have shown that ACEIs/ARBs exhibit ability to upregulate ACE 2 expression in addition to their main pharmacological effect to inhibit angiotensin‑converting enzyme 1 (ACE 1) or block angiotensin II type 1 receptor.

Considering that ACE 2 expression might correlate with the susceptibility to SARS‑CoV‑2, intake of ACEIs/ARBs might predispose patients to the infection of SARS‑CoV‑2. Therefore, some cardiologists have suggested that patients should discontinue ACEIs/ARBs to avoid the potential increased risk of SARS‑CoV‑2 infection. [23]

Contrary to this, there is evidence which shows that the activation of the renin‑angiotensin system (RAS) and the down-regulation of ACE 2 expression are involved in the pathological process of lung injury after SARS‑CoV infection. Recently, it has been reported that serum level of angiotensin II is significantly elevated in COVID‑19 patients and exhibits a linear positive correlation to viral load and lung injury.[24] Activation of the RAS can cause widespread endothelial dysfunction and varying degrees of multiple organ (heart, kidney, and lung) injuries. Thus, intake of ACEIs/ARBs might probably relieve the lung injury and absolutely decrease heart and renal damage resulting from the RAS activation.

Role of ACE 2 in the Cardiovascular system:

ACE 2 converts angiotensin II to angiotensin 1‑7. ACE 2 is a type I transmembrane protein, which is mainly anchored at the apical surface of the cell. Its catalytic domain is located at the extracellular side of the cell, which can be cleaved and released into blood by ADAM 17 (a disintegrin and metalloproteinase domain‑containing protein 17).[25]

The recombinant human ACE 2 (rhACE2), which is purified from the supernatant of ACE 2 transfected cells, can generate angiotensin 1‑7 from angiotensin II and shows the ability to prevent angiotensin II–induced myocardial hypertrophy, diastolic dysfunction, and myocardial fibrosis. But the role of cleaved ACE 2 in circulation is still unclear.

ACE 2/angiotensin 1‑7 axis is another arm of RAS, which generally shows the opposite effect to the ACE 1/angiotensin II axis.[25]

While angiotensin II can induce strong vasoconstriction, proinflammatory effects, and profibrotic effects; angiotensin 1‑7 exhibits antiproliferative, antiapoptotic, and mild vasodilating abilities and presents various cardiovascular protective effects, including anti–heart failure, antithrombosis, anti–myocardial hypertrophy, antifibrosis, antiarrhythmic, anti‑atherogenic, and attenuating vascular

dysfunction related to metabolic syndrome.

The disruption of the subtle balance between ACE 1 and ACE 2 can lead to the dysregulation of blood pressure. ACE 2 is widely expressed in cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells, which are also a regulator for heart function. Studies have found that over expression of ACE 2 can prevent or even reverse the heart failure phenotype, whereas loss of ACE 2 can accelerate the progression of heart failure. The activity of circulating ACE 2 in patients with heart failure is also significantly higher than in normal people, which is associated with poor prognosis. Shedding of the membrane-bound ACE 2 may be responsible for the increased circulating ACE 2 activity in patients with heart failure.

Role of ACE 2 in COVID-19:

SARS-CoV-2, as its name indicates, shares many similarities with SARS-CoV. SARS-CoV-2 uses the SARS-CoV receptor ACE 2 for host cell entry. It was retrospectively analysed in 425 confirmed cases of COVID-19, but very few cases occurred in children. [26] There is a possibility that it might be attributable to the difference in expression of ACE 2 between children and adults. Higher ACE 2 levels might be associated with a higher local viral load. It was found that the expression of ACE 2 was relatively higher in cells with higher pseudotype SARS-CoV-2 entry.

It has also been reported that higher initial viral load was associated with worse prognosis in SARS. A similar situation might also exist in COVID-19. However, no direct evidence has indicated a connection between ACE 2 expression and the susceptibility and severity of SARS-CoV-2 infection.

It has been reported that 3% to 20% of COVID-19 patients are combined with ARDS. [20, 21,22]

Recent studies have found that the RAS activation plays an important role in acute lung injury. ARDS animals showed reduced ACE 2 activity, and loss of ACE 2 can cause exaggerated neutrophil accumulation, enhanced vascular permeability, and exacerbated pulmonary oedema, which eventually lead to ARDS. Supplement of exogenous ACE 2 can attenuate the inflammatory response and increase oxygenation of tissues.

Potential heart Injury in COVID-19:

As with SARS, patients with COVID-19 also showed potential cardiac injuries. Chen et al reported that among the 99 confirmed COVID-19 patients admitted to Wuhan Jinyintan Hospital, 13 (13%) presented with elevated creatine kinase and 75 (76%) showed the elevation of lactate dehydrogenase.[20]

Wang et al described the clinical characteristics of 138 hospitalized COVID-19 patients at Zhongnan Hospital of Wuhan University and found elevated troponin I in 10 (7.2%), whereas 23 (16.7%) had arrhythmia.[21]

Besides, Guan et al extracted the data on 1099 COVID-19 patients from 552 hospitals in 31 provinces/provincial municipalities and found that 90 of 675 (13.7%) had an elevated creatinine kinase level and 277 of 675 (37.2%) showed an increased lactate dehydrogenase level.[22]

The myocardial dysfunction can be indirect, caused by reduced oxygen supply, severe lung failure, and the cytokine storm after the SARS-CoV-2 infection. However, there is also a possibility that it might be attributable to the decreased activity of ACE 2 in the heart, just like SARS.

Oudit et aL [27] detected the presence of SARS-CoV and a marked decreased ACE2 expression in the heart of intranasal SARS-CoV–infected mice. They also reported that SARS-CoV was isolated from 7 of the 20 human autopsy hearts, and the myocardial damage was accompanied by the decreased protein expression of myocardial ACE 2 as well. Recently, an autopsy case of COVID-19 was reported in Chinese.[28]

Liu et al observed a moderate amount of transparent light-yellow liquid in the pericardial cavity and mild epicardial oedema in an 85-year-old man who died from COVID-19. They also reported that the myocardial section was gray-red fish-like. If we consider that this old patient had a history of coronary heart disease, so whether the myocardial injury was associated with SARS-CoV-2 infection or not, is still unclear.

ACEIs/ARBs and ACE 2:

Several studies have shown that ACEIs/ARBs exhibit ability to upregulate ACE 2 expression in addition to their main pharmacological effect to inhibit ACE 1 or block the angiotensin II type 1 receptor. Enalapril can restore left ventricular ACE 2 expression levels in rats with heart failure. [7] Losartan and Olmesartan can increase the expression of ACE 2 mRNA in the heart of rats after myocardial infarction. It was found that lisinopril can increase the level of ACE 2 mRNA but not the activity of ACE 2 in the heart of normal Lewis rats, whereas losartan can simultaneously increase the mRNA expression as well as the protein activity of ACE 2 in the heart of Lewis rats.[6] However, the current research is mainly limited to the effects of ACEIs/ARBs on the changes of ACE 2 mRNA levels and activity in animal hearts. The effects of ACEIs/ARBs on ACE 2 mRNA levels and protein activity in human lung tissues are still unclear.

ACEIs/ARBs might play a dual role in COVID-19:

To sum up, the evidence at present shows that ACEIs/ARBs could increase the expression and activity of ACE2 in heart, performing the protective role in cardiovascular system. However, the impact of ACEIs/ARBs on ACE 2 in other organs, especially whether they could influence the expression level and activity of ACE2 in lungs, remains unknown. If ACEIs/ARBs do own the ability to upregulate the expression and activity of ACE 2 in lungs, they may play a dual role in COVID-19. On the one hand, the higher level of ACE 2 might increase the susceptibility of cells to SARS-CoV-2. On the other hand, the activation of ACE 2 might ameliorate the acute lung injury induced by SARS-CoV-2.

We now return to our initial question: Should we discontinue ACEIs/ARBs for patients who have been taking them for a long time in the context of COVID-19? The authors believe that the answer might be no. The use of ACEIs/ARBs might be a double-edged sword in COVID-19. On the one hand, it might lead to an increased risk of SARS-CoV-2 infection. On the other hand, it might reduce the severity of lung damage caused by the infection. However, it would be unwise to discontinue these medications assertively because the protective role of ACE 2 in the respiratory system is supported by ample evidence, whereas the increased danger of infection is still a hypothesis. Besides, patients with COVID-19 also showed potential cardiac injuries and the RAS activation. As shown in the Figure 2, the SARS-CoV-2 infection could possibly influence the balance between angiotensin II and angiotensin 1-7, whereas ACEIs/ARBs can block the RAS and protect the heart and other organs, which are susceptible to injury caused by the RAS activation.

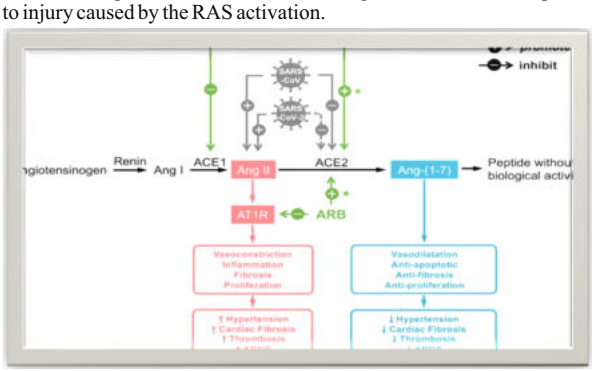


Figure 2:- Role of ACE 1 and ACE 2 in COVID-19

Diabetes in COVID-19:

The COVID-19 infection is a double challenge for people with diabetes. Diabetes has been reported to be a risk factor for the severity of the disease and at the same time, patients have to control glucose in this situation with a decreased and more variable food intake. Diabetes is a risk factor for hospitalisation and mortality of the COVID-19 infection. Diabetes was a comorbidity in 22% of 32 non-survivors in a study of 52 intensive care patients. [29] In another study of 173 patients with severe disease, 16.2% had diabetes, and in further study of 140 hospitalised patients, 12% had diabetes [30]

When comparing intensive care and non-intensive care patients with COVID-19, there appears to be a twofold increase in the incidence of patients in intensive care having diabetes. [31] Mortality seems to be about threefold higher in people with diabetes compared with the general mortality of COVID-19.

The number of comorbidities is a predictor of mortality in COVID-19. Indeed, people with diabetes are a high-risk group for severe disease. Notably, diabetes was also a risk factor for severe disease and mortality in the previous SARS, MERS (Middle East respiratory syndrome) coronavirus infections and the severe influenza A H1N1 pandemic in 2009. It is a fact that people with diabetes are at increased risk of infections including influenza and for related complications such as secondary bacterial pneumonia. Diabetes patients have impaired immune-response to infection, both in relation to cytokine profile and to changes in immune-response including T-cell and macrophage activation. [32] Poor glycaemic control impairs several aspects of the immune response to viral infection and also to the potential bacterial secondary infection in the lungs. [33] Many patients with type 2 diabetes are obese and obesity is also a risk factor for severe infection. Specifically, metabolic active abdominal obesity is associated with higher risks.[34]

The abnormal secretion of adipokines and cytokines like TNF-alfa and interferon characterise a chronic low-grade infection in abdominal obesity and may induce an impaired immune-response. People with severe abdominal obesity also have mechanical respiratory problems, with reduced ventilation of the basal lung sections increasing the risk of pneumonia as well as reduced oxygen saturation of blood. Obese subjects also have an increased asthma risk, and those patients with obesity and asthma have more symptoms, more frequent and severe exacerbations and reduced response to several asthma medications.

Lastly, late diabetic complications such as diabetic kidney disease and ischaemic heart disease may complicate the situation for people with diabetes, making them frailer and further increasing the severity of COVID-19 disease and the need for care such as acute dialysis. Some findings indicate that COVID-19 could cause acute cardiac injury with heart failure, leading to deterioration of circulation.[35]

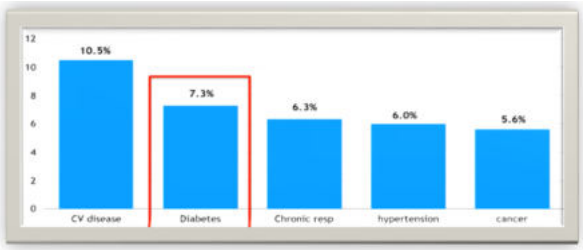


Figure 3:- Case fatality rate in COVID-19 associated with different comorbidities

Chronic respiratory diseases in SARS-CoV infection:

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an acute respiratory disease that can lead to respiratory failure and death.[36] Previous epidemics of novel coronavirus diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), were associated with similar clinical features and outcomes.[37]

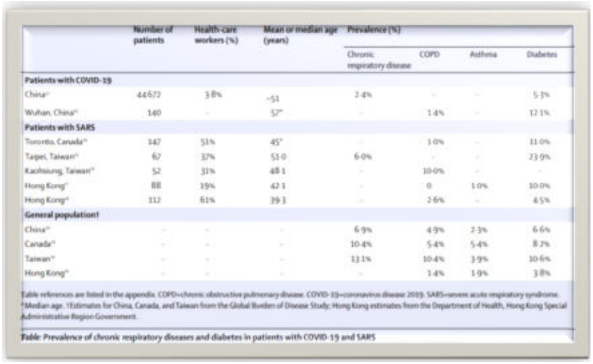
One might anticipate that patients with chronic respiratory diseases, particularly chronic obstructive pulmonary disease (COPD) and asthma, would be at increased risk of SARS-CoV-2 infection and more severe presentations of COVID-19. However, it is striking that both these diseases appear to be under-represented in the comorbidities reported for patients with COVID-19, compared with the prevalence of global burden of disease estimates of these conditions in the general population, similar to the pattern seen with SARS. By contrast, the prevalence of diabetes in patients with COVID-19 or SARS is as high as or higher than the estimated national prevalence, as might be expected. The lower reported prevalence of asthma and COPD in patients diagnosed with COVID-19 might be due to one or a number of factors. First, it is possible that, in contrast to the diagnosis of diabetes, there was substantial underdiagnosis or poor recognition of chronic respiratory disease in patients with COVID-19. However, this seems unlikely, as in very recent data (March 23, 2020) from Italy, among 355 patients dying with COVID-19 (mean age 79·5 years), diabetes was reported in 20·3% of patients but COPD was not listed as a comorbidity for any patient. [38] Similarly, provisional data from USA (March 31, 2020) show that chronic respiratory diseases and diabetes were comorbidities in 8.5% and 10.2% of patients with COVID-19, respectively, compared with global burden of disease figures for the population as a whole of 11·3% for chronic respiratory diseases and 10·2% for diabetes; however these data are based on only 7162 of the 74439 patients reported.[39]

A second possibility is that having a chronic respiratory disease protects against COVID-19, perhaps through a different immune response elicited by the chronic disease itself. However, this theory is not supported by the finding that among those with COVID-19 who have COPD as comorbidity, mortality is increased, as would otherwise be expected.[40]

A third possibility is that therapies used by patients with chronic respiratory diseases can reduce the risk of infection or of developing symptoms leading to diagnosis. It is important to note that, at most only around half of patients with COPD and asthma use inhaled corticosteroids. Furthermore, in in-vitro models, inhaled corticosteroids alone or in combination with bronchodilators have been shown to suppress coronavirus replication and cytokine production.[41] Low quality evidence also exists from a case series in Japan, in which improvement was seen in three patients with COVID-19 requiring oxygen, but not ventilatory support. Yet, the possibility that inhaled corticosteroids might prevent (at least partly) the development of symptomatic infection or severe presentations of COVID-19 cannot be ignored. By contrast, a systematic review on the use of systemic corticosteroids to treat SARS, once established, showed no benefit but possible harm. [42]

The potential benefits or harms of inhaled corticosteroids and other treatments for people at risk of SARS-CoV-2 infection or patients with COVID-19 are unclear at present, and no changes to the treatment or management of chronic respiratory conditions, including COPD and asthma, should be considered at this stage.

Table 3:- Comparison of prevalence of different comorbidities in COVID-19 and general population



	Number of patients	Health-care workers (%)	Mean or median age (years)	Prevalence (%)			
				Chronic respiratory disease	COPD	Asthma	Diabetes
Patients with COVID-19							
China[a]	44 672	3·8%	~51	2·4%	..	..	5·3%
Wuhan, China[b]	140	..	52*	..	1·4%	..	12·1%
Patients with SARS							
Toronto, Canada[c]	147	51%	45*	..	1·0%	..	11·0%
Taipei, Taiwan[c]	67	37%	53·0	6·0%	..	..	23·9%
Kaohsiung, Taiwan[c]	52	31%	48·1	..	10·0%	..	..
Hong Kong[c]	88	19%	42·1	..	0	1·0%	10·0%
Hong Kong[d]	112	61%	39·1	..	2·6%	..	4·5%
General population†							
China[e]	..	..	..	6·9%	4·9%	2·3%	6·6%
Canada[f]	..	..	..	10·4%	5·4%	5·4%	8·2%
Taiwan[g]	..	..	..	13·1%	10·4%	3·9%	10·6%
Hong Kong[h]	..	..	..	..	1·4%	1·9%	3·8%

Table references are listed in the appendix. COPD=chronic obstructive pulmonary disease. COVID-19=coronavirus disease 2019. SARS=severe acute respiratory syndrome. *Median age. †Estimates for China, Canada, and Taiwan from the Global Burden of Disease Study; Hong Kong estimates from the Department of Health, Hong Kong Special Administrative Region Government.

Table: Prevalence of chronic respiratory diseases and diabetes in patients with COVID-19 and SARS

COVID-19 in cancer patients:

Patients with cancer are a vulnerable population in the ongoing COVID-19 pandemic. They are at high risk of infection and have a higher probability of severe illness and increased mortality once diagnosed with COVID-19.

A multicentric, retrospective, cohort study was done in Wuhan, China to describe the clinical features, outcomes, and risk factors for mortality in patients with cancer, being diagnosed as COVID-19 positive. Severe pneumonia occurred in 52 (25%) patients and the in-hospital case-fatality rate in patients with COVID-19 and cancer was 20%, which was much higher than the case-fatality rate for COVID-19 in the overall Chinese population (1%).[43]

In Wuhan, the case-fatality rate of patients with cancer in a study was 18% (34 of 184 patients), which was higher than the overall case-fatality rate reported for patients with COVID-19 (8%). In particular, male sex and those receiving chemotherapy within 4 weeks before the symptom onset was identified as risk factors for death in patients with cancer who were diagnosed with COVID-19.

The proportion of patients with cancer among those with COVID-19,

who were admitted to the nine hospitals in a study was 2.5%, which was higher than that reported in the overall Chinese population (0.29%)[44] and in a previous report of patients with COVID-19 (1%).[45] This finding suggests that patients with cancer are more susceptible to COVID-19 than the general population.

We found bilateral lung lesions in 91% of patients with available records, which was higher than the figure reported previously by Xu and colleagues (bilateral lung lesions in 53 [59%] of 90 patients with laboratory-confirmed SARS-CoV-2 infection), suggesting that patients with cancer were more vulnerable once they became infected with SARS-CoV-2**.** Men were found to be at a higher risk of mortality than women in that study. In addition to sex differences in smoking rate,[46] differences in the immune and endocrine systems between men and women [47, 48] might exert different responses against SARS-CoV-2 infection. Moreover, case-fatality rates for patients with COVID-19 who had breast, thyroid, or cervical cancer were low in our study. 62 (57%) of 109 women in our study had one of these three types of cancers. Lymphocytopenia is one of the clinical features of COVID-19, indicating that the virus tends to diminish the antiviral immunity of the host.

Similar to other studies, we found that cytotoxic chemotherapy within 4 weeks before symptom onset was associated with increased risk of mortality. Patients receiving chemotherapy might develop long-lasting myelosuppression and impaired immunity. Since we do not yet have highly effective drugs targeting SARS CoV-2, a patient's inherent immunity might be a determining factor for their prognosis after effective supportive care. It has been recommended that the mode of administration (from infusion to oral administration) and intervals of chemotherapy should be adjusted according to patients'conditions.

Although molecular-targeted therapy rarely impairs patients' immunity, those receiving maintenance molecular-targeted therapy all had advanced disease, and seven (58%) of 12, had received chemotherapy concurrently within 4 weeks before symptom onset, which might have accounted for the increased risk of death in these patients.

Immunosuppressive treatments administered more than 4 weeks before symptom onset might not worsen the outcome of COVID-19, which can be partially explained by the recovery of patients from side-effects of cytotoxic treatments.

Many hematological malignancies change, how blood cells in the immune system function. Lower respiratory tract diseases caused by human coronaviruses in patients with haematological malignancies have been associated with high rates of oxygen use and mortality. In our study, patients with haematological malignancies had poorer prognoses than those with solid tumours. Besides the inherent differences between hematological malignancies and solid tumors, more patients with hematological malignancies received chemotherapy within 4 weeks before symptom onset (11 [55%] of 20 *vs* 20 [12%] of 162), which might partly explain the finding of worse outcomes in these patients.

In addition to lymphocytes, neutrophils are the mainstay in fighting off various infections. NLR is considered to reflect host inflammation and is a predictor of bacterial infection. It has also been found to be associated with clinical outcome and treatment efficacy in several cancers. In patients with COVID-19, high neutrophil counts have frequently been seen in refractory disease. In line with a previous study, we found a high NLR to be associated with poor prognosis in patients with cancer and COVID-19. SARS-CoV-2 infection and subsequent bacterial infection might have caused a deterioration of lung function and contributed to death, although this hypothesis requires further investigation.

In conclusion, patients with cancer and COVID-19 require urgent and special attention, since they are a vulnerable population with a much higher case-fatality rate than the general population. Receiving chemotherapy 4 weeks before symptom onset and male sex are two indicators that might help clinicians to identify patients with cancers, who are at high risk of fatal outcomes at an early stage.

Death rate : (number of deaths / number of cases) = probability of dying if infected by the virus (%). The percentages shown below do not add up to 100%, as they don't represent share of deaths by different age-groups. Rather, it represents the risk of dying, if infected with COVID-19 for a person in a given age-group.

Table 4:- Deate rate in COVID-19 associated with various comorbid conditions

PRE-EXISTING CONDITION	DEATH RATE confirmed cases	DEATH RATE all cases
Cardiovascular disease	**13.2%**	**10.5%**
Diabetes	**9.2%**	**7.3%**
Chronic respiratory disease	**8.0%**	**6.3%**
Hypertension	**8.4%**	**6.0%**
Cancer	**7.6%**	**5.6%**
no pre-existing conditions		**0.9%**

As we can see from above table, any co-morbidity increases the chances of death in a person confirmed with COVID-19.

CONCLUSION:

From the above data, it has been proven that people already living with some co-morbidity are worse affected by COVID-19 than people without comorbidities. Also, older age-group patients have more signs and symptoms. This is majorly because of the weak immune system in older people having co-morbidities.

As of cardiovascular diseases, the death rate increased from 10.5 % to 13.2 % which can mainly be attributed to the ACE 2 receptors of SARS CoV-2 in our body, which are upregulated by ACE inhibitors and AR blockers (drugs that are almost taken by all the patients of cardiovascular disorders). Death rate of patients with diabetes suffering from COVID-19 has increased 2% i.e. from 7.3% to 9.2 %. It is mainly because the poor glycemic index leads to poor immunity and decreases body's immune response towards the viral infection.

In the case of chronic respiratory diseases that include mostly asthma and chronic obstructive pulmonary disease, the death rates have increased from 6.3% to 8 %. Although, the signs and symptoms of these diseases mostly mimic that of COVID-19, this might lead to an under-estimation of the deaths due to the disease. Also, in some studies, it has been seen that corticosteroids taken mostly by the patients of chronic respiratory diseases might suppress the effects of coronavirus. In many other studies, it has been seen that patients of chronic respiratory diseases already have a certain amount of lung injury and so these are even worsened by the coronavirus superadded infection.

The increase of death rates in patients of malignancy infected with COVID-19 has increased from 5.6% to 7.6 %. Also, death rates among population with no preexisting condition is very less that is 0.9 % only.

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