COVID-19 severity in patients with diabetes and cardiovascular diseases: A Short Review

Houda EL ALAMI\textsuperscript{a, b}, Lahcen WAKRIM\textsuperscript{c} Hassan GHAZAL\textsuperscript{d}, Omar ABIDI\textsuperscript{f}, Naima KHLIL\textsuperscript{b}, Abderrahman NAAMANE\textsuperscript{b}, Abderahmane MAAROUFI\textsuperscript{f}, Salsabil HAMDI\textsuperscript{a}

\textsuperscript{a}Environmental Health Laboratory, Institut Pasteur du Moroc, Casablanca, Morocco
\textsuperscript{b}Laboratory of Chemistry, Biochemistry, Nutrition, and Environment, Faculty of Medicine and Pharmacy, University Hassan II, Casablanca, Morocco
\textsuperscript{c}Immunovirology laboratory, Institut Pasteur du Moroc, Casablanca, Morocco
\textsuperscript{f}CNRST Rabat, Morocco

\textsuperscript{1}INET Institut Supérieur des Professions Infirmières et Techniques de Santé (ISPITS) de Casablanca, Ministère de la Santé, Morocco.

\*Corresponding Author: Houda EL ALAMI & Salsabil HAMDI

1Environmental Health Laboratory, Institut Pasteur du Moroc, Casablanca, Morocco

\texttt{Houdaelalami14@gmail.com} / \texttt{salsabil.hamdi@pasteur.ma}

\begin{abstract}
A novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has been become a global health hazard and declared as a pandemic disease by WHO. Patients with Covid-19 and pre-existing medical conditions like cardiovascular diseases, diabetes mellitus and hypertension have an increased risk of severe disease and death. Furthermore, the increased expression of Angiotensin -converting enzyme 2 (ACE-2) in patients with diabetes or cardiovascular diseases could increase the risk of severe infection with SARS-CoV-2.
\end{abstract}

\section{Introduction}
Currently, the world is facing an outbreak of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11th, 2020, The World Health Organization declared this disease as pandemic (WHO Director-General’s, 2020). At the time of writing, the novel Coronavirus SARS-CoV-2 continues to spread, and it has infected more than 11,999,938 people worldwide and claimed 547,682 lives. In Morocco, 14,730 have been infected and 240 dead so far (Worldometers, 2020).
The spread of the COVID-19 has reached global pandemic proportions and it is a threat increase morbidity and mortality worldwide. Although the global mortality levels of the novel Coronavirus are low (1.4-2.3%), patients presenting with comorbidities such as overt diabetes, cardiovascular disease obesity and hypertension are more likely to be infected and are at a higher risk for complications and subsequent mortality from COVID-19 (Guan et al., 2020; Onder, Rezza and Brusaferro, 2020; Wu and McGoogan, 2020; J. Yang et al., 2020; Zhou et al., 2020).

SARS-CoV-2, like other members of the Coronaviridae family, is enveloped virus with positive-sense, single-stranded RNA, surrounded by a helical symmetry nucleocapsid (Su et al., 2016; Huang et al., 2020). Angiotensin-converting enzyme 2 (ACE-2) is a type I transmembrane glycoprotein that is strongly expressed in various organ systems including the kidney, cardiovascular system, lungs and brain (Tipnis et al., 2000; Patel et al., 2016). Like ACE-1, ACE-2 has 2 domains:

- The amino terminal catalytic domain shares 41.8% sequence identity with the amino domain of ACE (Donoghue et al., 2000; Tipnis et al., 2000).
- The carboxy terminal domain share 48% sequence identity with Collectrin. This domain has a critical role in amino acid reabsorption (Zhang et al., 2001; Tikellis and Thomas, 2012).

The enzymatic function of ACE-2 has non-catalytic actions including the regulation of intestinal neutral amino acid transport, renal amino acid transport and pancreatic insulin secretion. In addition, ACE-2 catalyzes the conversion of angiotensin II to angiotensin (1-7), thereby counterbalancing effects between ACE and ACE-2 (Tikellis and Thomas, 2012; Ras et al., 2018). In this context, the ACE-2/ Angiotensin (1-7) system plays an anti-inflammatory and anti-oxidant role protecting the lung against acute respiratory distress syndrome; as a matter of fact, ACE-2 has been found to be protective against lethal avian influenza A H5N1 infections (Zou et al., 2014).

In a similar way to the coronavirus that caused SARS, the new type of coronavirus responsible for COVID-19 uses ACE-2 on the surface of epithelial cells to bind and gain entry to infected cells (Hoffmann et al., 2020; Lu et al., 2020).

This review is aimed to understand the interaction between SARS-CoV-2 severity and chronic diseases (diabetes and cardiovascular diseases).

1. Diabetes mellitus and COVID-19

1.1 Diabetes mellitus (DM)

Globally, diabetes mellitus has become one of the most common chronic diseases not only in developed countries, but also in developing countries (Karino and Pace, 2012; IDF, 2019). The number of patients with diabetes mellitus has reached more than 451 million worldwide in 2017 and this number is predicted to increase to 693 million by 2045(Cho et al., 2018). This increase is probably related to lifestyle of the modern world such as unhealthy diet, overweight and obesity, sedentary, stress, smoking, intestinal microbiota dysbiosis and chemical exposure. In addition, there are genetic and epigenetic factors that favor the disease (Ng et al., 2014; Woldeamlak, Yirdaw and Biadgo, 2019; Yang et al., 2019).

Diabetes is associated with several complications, including high blood pressure, asthma, cardiovascular diseases, blindness, sleep apnea, gynecological problems (menstrual irregularities and infertility) and limb amputation, which often lead to morbidity and mortality (Condorelli et al., 2018; Kelsey et al., 2018; Siwasaranond et al., 2018).
1.2 Association between diabetes mellitus and COVID-19 severity

Individuals with diabetes mellitus have a higher susceptibility to some infectious diseases, like staphylococcus aureus and mycobacterium tuberculosis that results from multiple perturbations of innate immunity (Joshi et al., 1999; Shah and Hux, 2003; Hodgson et al., 2015). JK Yang et al. have shown that ambient hyperglycemia and diabetes mellitus are independent predictors for morbidity and mortality in sever acute respiratory syndrome patients (Yang et al., 2006). Furthermore, several studies (Table 1) have shown that patients with diabetes mellitus are more severely affected by COVID-19 and are at a higher risk for complications and death (Fang, Karakiulakis and Roth, 2020; Muniyappa and Gubbi, 2020; Wu et al., 2020). Yang X et al. showed that among the 32 non-survivors from a group of 52 intensive care unit patients with coronavirus disease 2019, DM (22%) was a predominant comorbidity (X. Yang et al., 2020). In another study reported by Guan et al., among 1099 COVID-19 confirmed patients, 173 who developed a severe disease have comorbidities including hypertension (23.7%), diabetes mellitus (16.2%), coronary heart diseases (5.8%), and cerebrovascular disease (2.3%) (Guan et al., 2020). In a study in 140 patients infected by SARS-CoV-2 in Wuhan, China, 30% had hypertension and 12% had diabetes (Zhang et al., 2020).

Interestingly, there was similarly an increased risk factor for mortality in patients with diabetes mellitus infected with Pandemic Influenza (H1N1) in 2009, Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory syndrome-related coronavirus (MERS CoV) in 2012 (Yang et al., 2006; Knapp, 2013; SID, 2018; Song et al., 2019). However, a recent summary report from the Chinese Center for Disease Control and Prevention, showed that among 72,314 COVID-19 cases across the country an increased mortality was observed in people with diabetes mellitus (2.3% vs. 7.3% overall) (Wu and McGoogan, 2020).

It is currently unknown why people living with diabetes mellitus are more at risk of developing severe symptoms and complications if they are infected by SARS-CoV-2, but one possible explanation involves ACE-2. ACE-2 is the gateway for the SARS-CoV-2 to penetrate in the human cells. The latter is largely expressed in the liver and the endocrine pancreas with a potential role in the development of insulin resistance and impaired insulin secretion (Bindom and Lazartigues, 2009; Hoffmann et al., 2020; Lu et al., 2020).

Patients with diabetes mellitus are treated with ACE inhibitors and angiotensin receptors blockers, which can cause increased expression of ACE-2, and consequently can could theoretically increase the risk of severe infection with SARS-CoV-2 (Fang, Karakiulakis and Roth, 2020).
Table I. Results of main retrospective and meta-analysis studies of COVID-19.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Simple size</th>
<th>Age</th>
<th>Male/female</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>CVD</th>
<th>Cerebrovascular diseases</th>
<th>Coronary artery diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al., 2020</td>
<td>191</td>
<td>56(46-67)</td>
<td>119/72</td>
<td>36 (19%)</td>
<td>58(30%)</td>
<td>-</td>
<td>15 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>Wang et al., 2020</td>
<td>138</td>
<td>56(42-68)</td>
<td>75/63</td>
<td>14 (10.1%)</td>
<td>43 (31.2%)</td>
<td>20 (14.5%)</td>
<td>7 (5.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Huang et al., 2020</td>
<td>41</td>
<td>49(41-58)</td>
<td>30/11</td>
<td>8 (19.5%)</td>
<td>6 (14.6%)</td>
<td>6 (14.6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guan et al., 2020</td>
<td>1099</td>
<td>47(35-58)</td>
<td>640/459</td>
<td>81 (7.3%)</td>
<td>165 (15.0%)</td>
<td>-</td>
<td>15 (1.4%)</td>
<td>27 (2.5%)</td>
</tr>
<tr>
<td>Liu et al., 2020</td>
<td>137</td>
<td>57(20-83)</td>
<td>61/76</td>
<td>14(10.2%)</td>
<td>13(9.5%)</td>
<td>10 (7.3%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wu et al., 2020</td>
<td>201</td>
<td>51(43-60)</td>
<td>128/73</td>
<td>22 (10.9%)</td>
<td>39 (19.4%)</td>
<td>8 (4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Chen et al., 2020)</td>
<td>99</td>
<td>55.5(13.1)</td>
<td>67/32</td>
<td>12 (12.1%)</td>
<td>-</td>
<td>40 (40%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ruan et al., 2020</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>25(16.7%)</td>
<td>52(34.7%)</td>
<td>13(8.7%)</td>
<td>12 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>X. Yang et al., 2020</td>
<td>52</td>
<td>59.7(13.3)</td>
<td>35/17</td>
<td>9 (17%)</td>
<td>-</td>
<td>5 (10%)</td>
<td>7 (13.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Xu et al., 2020</td>
<td>62</td>
<td>41(32-52)</td>
<td>35/27</td>
<td>1(2%)</td>
<td>5 (8%)</td>
<td>-</td>
<td>1(2%)</td>
<td>-</td>
</tr>
<tr>
<td>Fang et al., 2020</td>
<td>2866</td>
<td>-</td>
<td>-</td>
<td>206 (7.3%)</td>
<td>376 (13.3%)</td>
<td>233 (8.3%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

2. Cardiovascular disease and COVID-19

2.1 Cardiovascular diseases

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in worldwide, as well as a major cause of disability (Institute for Health Metrics and Evaluation., 2013). Cardiovascular disease is a term that encompasses a wide range of disorders of heart and circulatory systems such as hypertension, heart failure, coronary heart disease, stroke, rheumatic heart disease and cardiomyopathy (British Heart Foundation, 2019).

Cardiovascular diseases are the number one cause of death worldwide. In 2015, approximately 17.9 million deaths from cardiovascular diseases, representing 31% of all global death. Of these deaths, 85% are due to heart attack and stroke (Roth et al., 2017; WHO, 2017).

2.3 Association between CVD and COVID-19 severity

Much like any other respiratory tract infection, including the severe acute respiratory syndrome and the middle East respiratory syndrome (Yang et al., 2006; Badawi and Ryoo, 2016), Patients with Cardiovascular diseases may predispose to COVID-19 infection and have an elevated risk of adverse outcomes. Furthermore, the infection with SARS-CoV-2 can also cause many indirect effects relevant to cardiovascular health (Li et al., 2020; Zhou et al., 2020). The prevalence of Cardiovascular diseases in patients with COVID-19 is marked by a variation in by region (Table I).

A meta-analysis of six published studies including 1527 patients with COVID-19 reported that the proportions of diabetes, cerebrovascular disease and hypertension...
were 9.7%, 16.4% and 17.7% respectively in China (Li et al., 2020).

ACE-2 plays an important role in the control of cardiac physiology, and altered ACE-2 expression or activity is linked to the progression of heart disease. In the heart, ACE-2 is expressed in the cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells (Tipnis et al., 2000; Gallagher, Ferrario and Tallant, 2008). However, the higher expression of ACE-2 in individuals with cardiovascular disease and hypertension might also lead to higher risk of SARS-CoV-2 infection (Zheng et al., 2020). Considering the favorable effects of ACE inhibitors and Ang II-receptor blockers (ARBs) on the control of the progression of cardiovascular diseases and hypertension, it was suggested that ACE inhibitors and ARBs may increase the risk of COVID-19 infection by up-regulating ACE-2.

**Conclusion**

In summary, it is appearing that patients with chronic complications (diabetes, Cardiovascular diseases) are at increased risk for COVID-19 infection, and have an increased risk for medical complications and death. It is important for people with pre-existing medical conditions (diabetes mellitus, cardiovascular disease and hypertension) to take precautions to avoid the SARS-CoV-2 if possible. The recommendations which are widely disseminated to the general public are doubly important for patients with diabetes or cardiovascular diseases and for anyone in close contact with patients with pre-existing medical conditions.

**Conflicts of Interest**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**

- Hodgson, K. et al. (2015) ‘Immunological mechanisms contributing to the double burden of diabetes and


• Xu, X.-W. et al. (2020) ‘Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series’, *BMJ (Clinical research ed.)*, 368, p. m606. doi: 10.1136/bmj.m606.


