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ORIGINAL ARTICLE

# Overview on cardiometabolic associated factors in COVID-19 patients': a narrative review

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## Abstract

Coronavirus disease 2019 (COVID-19) increases the risk of several cardiovascular diseases (CVDs) such as acute myocardial injury. Vascular dysfunctions are important drivers of CVDs. A variety of risk factors promotes the development and progression of CVDs including, overweight and obesity, arterial hypertension, physical inactivity, smoking, unhealthy diet, overconsumption of alcohol, dyslipidemia, atherosclerosis and diabetes mellitus. However, nearly all of these risk factors are modifiable by antihypertensive, antidiabetic, or lipid-lowering medication and lifestyle changes. Other factors such as age or genetic factors cannot be modified. Moreover, infection and inflammation have been shown to increase the risk of CVDs. The COVID-19 pandemic yielded a new perspective to this field. Cardiometabolic events, diseases, risk factors and COVID-19 are strongly intertwined. An increased CVDs risk through multifactorial mechanisms has been observed in COVID-19 patients. Furthermore, a higher rate of infection with COVID-19, severe COVID-19, and bad outcome has been demonstrated in patients with established cardiometabolic disorders and vascular risk factors. Summary at present, we suggest that regular interactions between healthcare professionals and patients should include education on COVID-19 and on primary and secondary vascular prevention in order to minimize the burden of the virus in our susceptible populations.

**Keywords:** Cardiometabolic disorders, cardiovascular diseases, inflammation, atherosclerosis, COVID-19.

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## 1 Introduction

In December 2019, a cluster of patients with unknown cause pneumonia was identified in Wuhan (China). The cause was then attributed to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that was then called COVID-19 "Coronavirus Disease 2019" and spreading rapidly from China to 215 countries in few weeks [1-3]. Therefore, the world's population was found facing the extraordinary challenge of an unrecognized and highly infectious viral disease [2].

The number of individuals being diagnosed with COVID-19 has increased steeply along with the pandemic pervasive. Until December 10, 2020, about 68.16 million confirmed cases and 1.55 million deaths from COVID-19 were reported (Figure 1) [3]. The spectrum of COVID-19 appears to lie from asymptomatic or mild viral illness to a systemic disease characterized by pneumonia, headache, fever, breathing difficulties (dyspnea), dry cough, anosmia and occasional diarrhea [4]. Cardiometabolic disorders have been described among the most important chronic underlying conditions worsening COVID-19 outcomes [5,6], with arterial hypertension, obesity, physical inactivity, dyslipidemia and diabetes mellitus being frequent comorbidities in patients with COVID-19 who require intensive care or die [7].

In this short review, we examined what is known concerning the possible comorbidities that may be risk factors for a more severe clinical course as well as mortality of COVID-19. It should be pointed out that some of the information mentioned below is based on the best judgment of endocrinologists and physicians with the first-hand experience in the care of such patients and some results of extensive clinical trial data.

## 2 COVID-19 and the cardiovascular system

It is well documented that the influenza infections, as well as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) viruses, can provoke cardiovascular complications that are usually represented in the form of myocarditis, acute myocardial infarction, acute heart failure, arrhythmia, subclinical diastolic impairment and cardiac arrest [8,9]. Like in previous Coronavirus outbreaks, the available data suggests that COVID-19 is related to numerous cardiovascular complications by increasing the risk of chronic cardiovascular damage especially in the older population and those who already have chronic conditions [10]. According to the analysis of Emami *et al.*, hypertension, cardiovascular diseases (CVDs), diabetes, chronic obstructive pulmonary disease,



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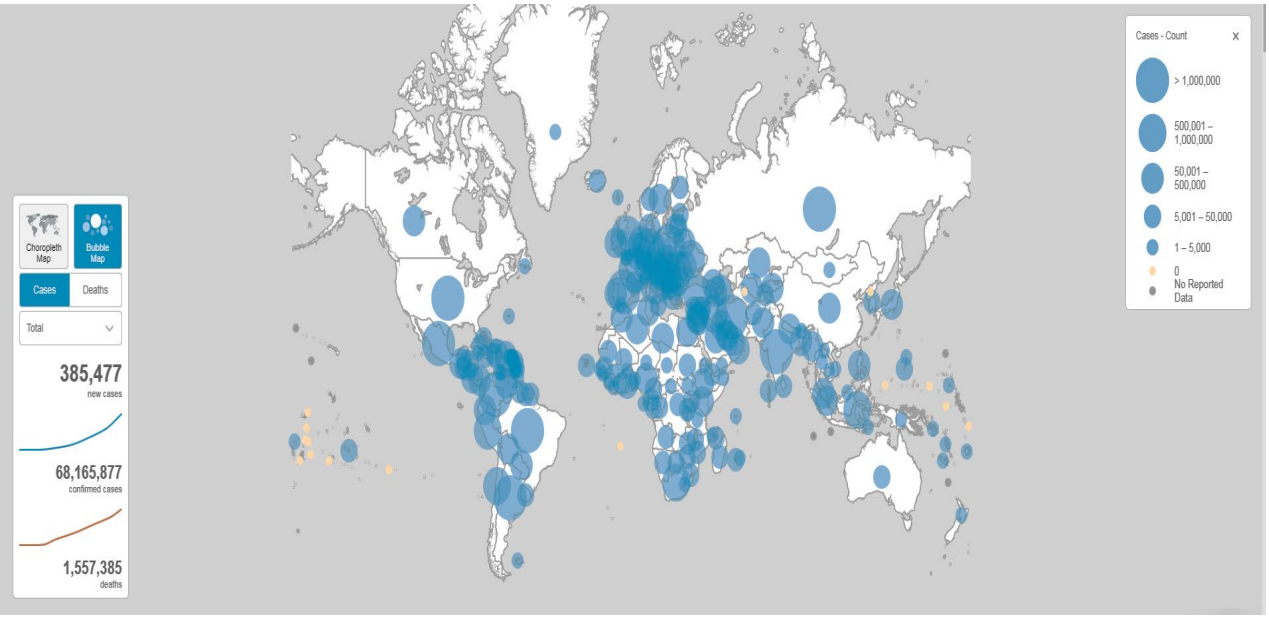


**Figure 1:** Novel Coronavirus (COVID-19) Situation in the World (World Health Organization, WHO) [3]

smoking, and kidney disease were the most prevalent underlying diseases among hospitalized patients with COVID-19. Of these, CVDs had the highest prevalence among diseases that put patients at higher risk from COVID-19 [11].

## 3 Risk factors related to cardiovascular complications in COVID-19

Cardiovascular risk factors are common among COVID-19 patients. Some of them are modifiable while others not (table 1).

**Table 1:** Summary of risk factors for cardiovascular complications in COVID-19

| Modifiable risk factors | Non-modifiable risk factors |
|---|---|
| - Overweight and obesity<br>- Arterial hypertension<br>- Physical inactivity<br>- Smoking<br>- Unhealthy diet and overconsumption of alcohol<br>- Dyslipidemia<br>- Atherosclerosis<br>- Diabetes mellitus | - Advanced age<br>- Male sex |

### 3.1 Age and sex differences

Statistics suggest that the patients above 60 years of age are at higher risk from development of cardiovascular complications. Data from China reveals that only 0.5% of patients in their 40's died from COVID-19, while the death rate increases with age (3.6% in 60 s, 8% in 70 s and 15% in 80 s). However, in Italy, the lethal outcome was seen in 25% of patients in their 70's and 31% in their 80's [12]. Reports from Italy revealed that cardiovascular comorbidities were the most commonly linked with the risk of death of COVID-19, most notably hypertension (70%), ischemic heart disease (30%), atrial fibrillation (20%), and heart failure (15%) [13]. It is interesting to notice that the male/female ratio of lethality is above 1.1, going to 1.7 in some European countries [12]. There have been several speculative theories to explain such differences including that women in middle age tend to have preferential lipid profile as compared to men of the same age partly due to the protective effects of female hormones.

The masculine hormone "testosterone" has been shown to have an immunosuppressive effect by inhibiting the differentiation of T-helper cells while estrogen has an immunostimulating impact[14]. Likewise, the reactivity toward influenza vaccine is reduced under the influence of testosterone[15]. Accordingly, various suggestions indicate that estrogen receptors play an effective role in COVID-19 infection and the higher rate of mortality rate and this could also be one of the reasons why females show a fast recovery and a low death rate from COVID-19. In contrast, there is no clear role for androgens in causing the disease [16].

Consequently, it is possible that CVD is more prevalent in men, and that patients with already existing CVD have a higher risk of complications during COVID-19 infection [13]. In addition, experimental studies have shown that estrogens can up-regulate the expression of Angiotensin-Converting Enzyme 2 (ACE2) in the female heart tissue. This may increase the port of entry for the virus but can significantly limit the subsequent inflammatory response and cytokine storm [17].

### 3.2 Overweight and obesity

Overweight is associated with arterial hypertension, dyslipidemia, inflammation, diabetes mellitus, endothelial dysfunction, hypercoagulability and cardiac arrhythmia, which all increase vascular risk. Furthermore, obesity can restrict ventilation, diminish diaphragm excursion, forced respiratory

volume, forced vital capacity, and impair the immune response to viral infections [18]. The COVID-19 pandemic increases the risk of obesity, by social distancing, lockdown policies, economic downturn, reduced physical activity, and changes of lifestyle [19]. There is evidence that obesity/overweight increases the risk of severe COVID-19. A descriptive multicenter study (n = 1687) found that patients who were overweight (BMI 25-29.9 kg/m$^2$, OR 1.32, 95%CI 1.03-1.69; p= 0.05), or had mild-to-moderate obesity (BMI = 30-39.9 kg/m$^2$, OR 1.8, 95% CI 1.39-2.35; p = 0.05), or had morbid obesity (BMI = 39-40 kg/m$^2$, OR 1.74, 95% CI 1.08-2.8; p = 0.05) were likelier to have severe COVID-19 vs. patients with normal weight [20]. Overall, obese individuals are a special risk group of patients in terms of having more severe COVID-19 thus more severe cardiovascular complications [21]. In addition, Wnt/β-catenin signaling pathway has been suggested to be an essential mechanism underlying the regulation of myofibroblast differentiation of lung-resident mesenchymal stromal/stem cells (MSCs) participated in the development of pulmonary fibrosis [22]. Hence, COVID-19 patients with obesity may suffer a more severe lung injury with pulmonary fibrosis owing to loss or dysfunctional lung resident MSCs induced by obesity. These MSCs in individuals with obesity may not be able to defend SARS-CoV-2 by modulating the immune response, tissue repair and homeostasis, and anti-inflammation. Conversely, obese MSCs may further increase systemic inflammation and negatively affect the immune response [23].

### 3.3 Arterial hypertension

As hypertension is strongly age related, the data could simply be confounded by age. Hypertension results in a number of pathophysiological changes in the cardiovascular system such as left ventricular hypertrophy and fibrosis. This may turn the hypertensive heart particularly susceptible to COVID-19 [24]. A recently published meta-analysis that involved 1576 patients of whom 280 with severe COVID-19 demonstrated that hypertension, was the most prevalent vascular risk factor in these patients (21.1%, 95% CI = 13.0-27.2%) [25]. Another study conducted on 1012 patients with COVID-19 showed that hypertension was more frequent in patients with aggravation of disease comparing with those who did not experience any deterioration of COVID-19 [26]. Additionally, a role has been postulated for ACE2 which is the binding site and entry receptor of SARS-CoV-2 [27]. In patients with arterial hypertension, ACE2 levels are increased in the blood, and this result in enhanced angiotensin II effects. SARS-CoV-2 leads to a partial decrease in ACE2 function, which also leads to enhanced angiotensin II effects [28]. Angiotensin II triggers inflammation, cell proliferation, hypertrophy, fibrosis and tissue remodeling through angiotensin 1 (AT1) receptor (so-called ACE/angiotensin II/AT1 receptor axis) [29]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which are frequently prescribed as antihypertensive drugs, increase the expression of ACE2 in tissue. They have been discussed to have a potentially wavy, protective and/or biphasic impact on COVID-19 [28]. Elevated expression of ACE2 in tissue may antagonize some detrimental effects of SARS-CoV-2. However, ACEIs/ARBs might negatively affect infection risk and outcome by increasing binding sites. A biphasic effect might be explained by the different phases of acute infection, which have been shown in COVID-19 [28].

### 3.4 Physical inactivity

Physical inactivity has a negative impact on weight, blood pressure and glucose, leading to dyslipidemia, anxiety/depression and systemic inflammation, which all increase vascular risk [30]. Social distancing and lockdown policies might impede personal instead of public transportation and thus decrease physical activity. Interestingly, a survey conducted by Rogers *et al.*, found that a lessening of physical activity throughout lockdown was associated with overweight, arterial hypertension, pulmonary disease, depression, and disability [31]. Likewise, a prospective cohort study (n = 387,109 of whom 760 had severe COVID-19) showed physical inactivity to be a risk factor for COVID-19 [32]. Thus, physical activity might help to prevent infection and severity of COVID-19 by downregulating the cytokine storm syndrome that befalls in some patients [33].

### 3.5 Smoking

Smoking probably has increased during the COVID-19 pandemic due to stress, anxiety and fewer possibilities of outdoor physical and other activities [34]. Moreover, smoking has been shown to influence the outcomes of COVID-19 by upregulating the expression of ACE2 [35]. A meta-analysis including a total of 2473 confirmed COVID-19 patients (current and ex-smokers) reported that current smokers were more likely to have severe COVID-19 compared with former and never smokers [36]. Hamer *et al.* also found that smoking to be a risk factor for COVID-19[32]. Furthermore, smoking increases the hardening of the arteries and produces an atherogenic lipid profile which can accelerate CVD[37].

### 3.6 Unhealthy diet and overconsumption of alcohol

Dietary habits and nutritional status have changed during the COVID-19 pandemic due to lockdown, social distancing, and economic downturn that have affected grocery shopping which leads people to favor long-lasting and less healthy foods. An electronic questionnaire (n = 1047) revealed that nutrition patterns during lockdown (number of main meals, intake of snacks between meals, eating out of control, and type of food) were unhealthier [38]. Due to anxiety of future food shortage, it is plausible that people will purchase packaged and long-life food rather than fresh food. This leads to weight gain and to a reduced intake of antioxidants. Oxidative stress and mild chronic vascular inflammation are part of the pathophysiology of hypertension and atherosclerosis [39]. As some people started experiencing more mental health problems than normally, it is likely that some increased their intake of alcohol [40]. On the other hand, people with an established Alcohol Use Disorder (AUD) might require particular considerations due to their greater vulnerability to lung infections [41]; besides, an atypical manifestation of COVID-19 might be mistaken for alcohol consumption leading to a diagnostic delay [42].

### 3.7 Dyslipidemia

Dyslipidemia is known to compromise the immune response and can lead to a maintained chronic inflammatory state, which leads to high cardiovascular risk [43, 44]. Furthermore, lipid metabolic demands increase due to virally caused acute inflammation result in a decreased myocardial oxygenation, ischemic damage, and vascular dysfunction with thrombotic complications [38]. Moreover, a meta-analysis (n = 1576, 1223 with severe COVID-19) showed a significant association of dyslipidemia with enhanced risk of severe COVID-19 infection, with high heterogeneity [RR 1.39 (95% CI 1.03-1.87), p = 0.03] [44].

### 3.8 Atherosclerosis

Numerous global reports on the clinical characteristics of patients with COVID-19 suggest increased vulnerability due to pre-existing cardiometabolic factors. An endothelial dysfunction is the common link between various predisposing cardiovascular or metabolic conditions; therefore, a pre-existing deregulation may represent an independent risk factor of the infection severity [45, 46]. Atherosclerosis is a cardiovascular system pathology that shares risk factors such as hypertension and diabetes with severe COVID-19 infections. It is a chronic inflammation of the endothelium characterized by infiltration, deposition and lipoproteins particles oxidation [46]. According to Vinciguerra *et al.* [47], atherosclerosis aggravates the immune system degradation resulting from an overactivation of pro-inflammatory patterns. Thus, a higher viral replication capacity of Coronavirus COVID-19 in human cells [47]. A strong hypothesis suggests that the severity of COVID-19 is influenced by atherosclerotic progression in susceptible patients, due to a large amount of immune system cells that are involved in organ damage. In contrast, the body's aberrant inflammatory response towards coronavirus attack, can lead to progression of atherosclerotic disease, thus increasing the risk of instability and rupture. The pathogenic correlation relationship between atherosclerosis and COVID-19 is simplified in Figure 2 [47].

### 3.9 Diabetes Mellitus

In parallel with COVID-19, the long-lasting global epidemic (diabetes) continued to affect more and more adult (aged 20 to 79 years) with 463 million cases during the year 2019, representing then 9.3% of the world's population and resulting in an overall expenditure burden of around $ 760 billion and about 4.2 million deaths in the same year [48]. Diabetes mellitus (DM) has been recognized as a primary risk factor for the development of severe pneumonia due to respiratory viral infections [49]. A reciprocal interaction has been identified between COVID-19 and diabetes [50]. Infection with COVID-19 leads to increased levels of blood inflammatory mediators such as lipopolysaccharide,

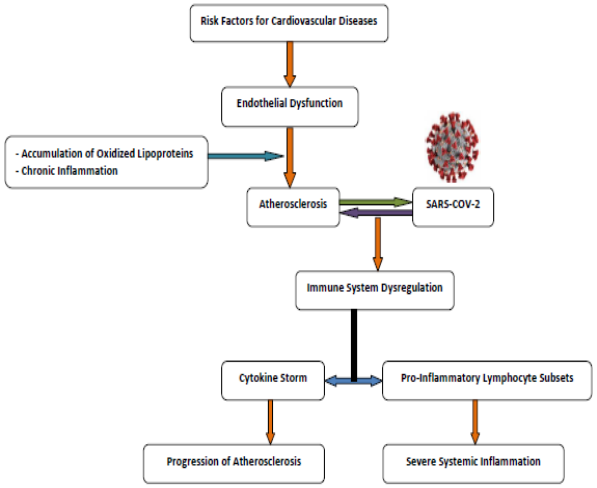


**Figure 2:** Proposed correlation relationship between atherosclerosis and COVID-19 [47]

inflammatory cytokines, toxic metabolites and to the production of reactive oxygen species (ROS). Likewise, a modification in the activity of natural killer cells and the production of IFNγ results in an upsurge in the interstitial and/or vascular permeability of the pro-inflammatory products. These effects represent the main cause of pulmonary fibrosis, acute lung injury and acute respiratory distress syndrome (Figure 3) [51]. Insulin resistance, hyperglycemia and vascular endothelial damage (as major causes of cardiovascular events), are all due to the ROS production and viral activation of the Renin-Angiotensin-Aldosterone System (RAAS) (by an increased angiotensin II expression) [51,52].COVID-19 infection also causes increased blood viscosity and endothelial damage which is responsible for cardiovascular events through increased coagulation components fibrinogen and D-dimer [51].

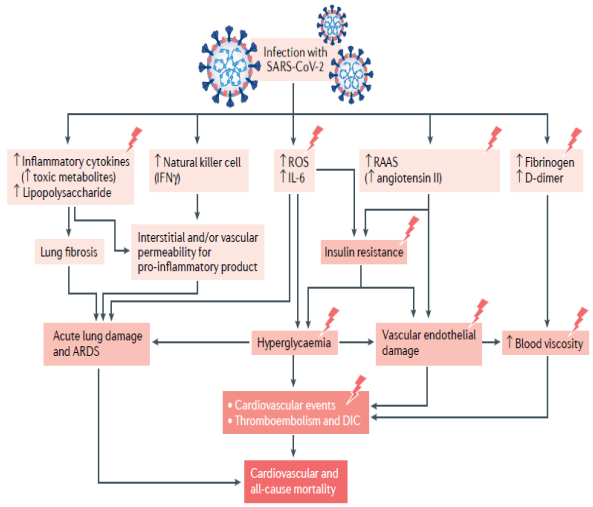


**Figure 3:** Potential pathogenic mechanisms in patients with type 2 diabetes and COVID-19 [51]

## 4 Conclusions

Multiple studies reveal a strong association between cardiovascular system, obesity, hypertension, dyslipidemia and diabetes mellitus—and COVID-19. COVID-19 patients with cardiometabolic risk factors have an enhanced hospitalization rate, more severe progression, and worse clinical outcomes. Apart from cardiovascular-related comorbidities, systemic chronic inflammation, deregulated metabolism, dysfunctional immune system, and impaired inflamed endothelium play crucial roles in bridging CVDs to critically severe outcomes of COVID-19. Therefore, it is strongly recommended that patients should strictly adhere to the recommendations of their healthcare professionals by consistent monitoring and primary vascular assessment which might decrease the burden of the virus.

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