

## REVIEW PAPER

# COVID-19 and arterial hypertension: Hypothesis or evidence?

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## Abstract

Investigations reported that hypertension, diabetes, and cardiovascular diseases were the most prevalent comorbidities among the patients with coronavirus disease 2019 (COVID-19). Hypertension appeared consistently as the most prevalent risk factors in COVID-19 patients. Some investigations speculated about the association between renin-angiotensin-aldosterone system (RAAS) and susceptibility to COVID-19, as well as the relationship between RAAS inhibitors and increased mortality in these patients. This raised concern about the potential association between hypertension (and its treatment) and propensity for COVID-19. There are only a few follow-up studies that investigated the impact of comorbidities on outcome in these patients with conflicting findings. Hypertension has been proven to be more prevalent in patients with an adverse outcome (admission in intensive care unit, use of mechanical ventilation, or death). So far, there is no study that demonstrated independent predictive value of hypertension on mortality in COVID-19 patients. There are many speculations about this coronavirus and its relation with different risk factors and underlying diseases. The aim of this review was to summarize the current knowledge about the relationship between hypertension and COVID-19 and the role of hypertension on outcome in these patients.

## 1 | INTRODUCTION

The first case of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, Hubei Province, China, on December 31, 2019. Until March, coronavirus disease 2019 (COVID-19), caused by this virus, has spread around the world. SARS-CoV-2 is human coronavirus, which does not belong to the group of benign coronaviruses that cause common cold, but to the smaller group of coronaviruses that cause acute respiratory distress syndrome (severe acute respiratory syndrome coronavirus—SARS and the Middle East respiratory syndrome coronavirus—MERS).<sup>1,2</sup>

Recently published studies showed that arterial hypertension, diabetes, cardiovascular diseases, and chronic obstructive pulmonary disease were prevalent among the patients with COVID-19.<sup>3-19</sup> Investigations on the outcome of these patients are scarce, and data are very limited. Nevertheless, hypertension is considered as one of the most important risk factors for COVID-19. The relationship between hypertension and adverse outcome is still questionable.

The aim of this review paper was to summarize current knowledge about the relationship between hypertension and COVID-19 and the role of hypertension in outcome of these patients. A comprehensive search was performed on PubMed, Scopus, Web of science, and Google scholar, to find review papers on this topic published until May 1, 2020.

## 2 | PATHOPHYSIOLOGICAL LINK BETWEEN COVID-19 AND CARDIOVASCULAR DISEASES

SARS-CoV-2 infection is triggered when the S-protein of the virus binds to angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the heart, lungs, kidney, and gastrointestinal tract, and plays an important role in several cardiovascular and immune pathways.<sup>20</sup> SARS-CoV-2 binds to ACE2 with much higher affinity compared to SARS-CoV.<sup>21</sup> Additionally, SARS-CoV-2 shows its pathogenic activity by attacking type II alveolar epithelial cells that are expressing ACE2. Previous studies of coronavirus that causes SARS demonstrated that this virus binds to ACE2 in pulmonary alveoli through their superficial spike proteins, which causes lung damage and even lung function failure.<sup>21</sup>

The loss of ACE2, caused by binding SARS-CoV-2, may shift the system to an overall higher angiotensin II and lower angiotensin-(1-7) tone. The role of angiotensin II in COVID-19 hypertensive patients seems to be crucial due to its role in functioning of the renin-angiotensin-aldosterone system (RAAS) that promotes vasoconstriction, sodium retention, oxidative stress, inflammation, and fibrosis and increases the bioactive peptide angiotensin-(1-7).<sup>22</sup>

## 3 | PREVALENCE OF HYPERTENSION IN PATIENTS WITH COVID-19

Epidemiological data coming from China indicate that arterial hypertension, cardiovascular diseases, diabetes, and chronic obstructive pulmonary disease are the most prevalent concomitant diseases in patients with COVID-19<sup>3-19,23</sup> (Table 1). The number of investigations that provided at least short follow-up with intrahospital outcome is limited. Even though these data demonstrated that the prevalence of hypertension in COVID-19 patients with lethal outcome was high,<sup>7-10,14,17</sup> it has still been debated whether hypertension was a predictor of mortality independently of other cardiovascular risk factors (age, obesity, diabetes) and comorbidities (coronary artery disease, heart failure, atrial fibrillation, cerebrovascular disease, renal impairment).

The prevalence of hypertension among patients with COVID-19, between different studies, ranged from 15%-20%<sup>3,4,11,12,16,17</sup> to 30%-35%.<sup>5-7,9,13</sup> There are several reasons for these variations. Average age was significantly higher in patients with elevated prevalence of hypertension,<sup>3-7,13-16</sup> which might be the most important reason for different prevalence of hypertensive patients among studies. Advanced age was associated with higher prevalence of other comorbidities such as diabetes, renal impairment, arterial hypertension, and obesity, which altogether increased proportion of hypertensive patients.<sup>5,6,9,13,15</sup>

The prevalence of overweight and obesity was not reported in available studies about COVID-19. This "circulus vitiosus" between hypertension, obesity, and diabetes is difficult to break, and therefore, conclusion cannot be made without detailed data of all links of

chain. The impact of smoking should not be forgotten in the relation between COPD, hypertension, and higher propensity to COVID-19.<sup>3,6-9,11,12</sup> However, results are conflicting, but majority of authors did not find higher prevalence of smoking in patients with adverse outcome.<sup>7-9</sup> The level of renal damage cannot be excluded as one of contribute factor for higher percentage of hypertension and advance stage of COVID-19 in hypertensive patients. Most of studies reported the large prevalence of cardiovascular diseases in COVID-19 patients, but they also did not classified them and therefore it is difficult to estimate the individual effect of coronary artery disease, heart failure, and atrial fibrillation on occurrence and severity of COVID-19.

Li et al summarized the findings from 6 studies and showed that the prevalence of hypertension, cardio-, and cerebrovascular disease and diabetes in patients with COVID-19 was 17.1%, 16.4%, and 9.7%, respectively.<sup>17</sup> The incidences of hypertension, cardio-cerebrovascular diseases, and diabetes were two- to threefolds higher in patients with severe type of COVID-19 than in their non-severe counterparts. Yang et al included 46,248 COVID-19 patients from 8 studies and reported that the most prevalent comorbidities were hypertension, diabetes, cardiovascular diseases, and respiratory system disease.<sup>18</sup> The most frequent comorbidities in severe patients were hypertension, respiratory system disease, and cardiovascular disease. The large meta-analysis that included 76,993 patients with COVID-19 found that the pooled prevalence of hypertension, cardiovascular disease, smoking history, and diabetes was 16.37%, 12.11%, 7.63%, and 7.87%, respectively<sup>19</sup> (Table 1). The authors of meta-analyses agreed about the large heterogeneity between studies, which obviously limited the quality of their study. This can be partly explained by different designs and large variation in sample size among studies.<sup>18,19</sup>

Some essential data are still missing, and it would be dangerous to ascribe the large portion of risk for SARS-CoV-2 infection or severity of COVID-19 to any risk factor, including hypertension. It would be reasonable to hypothesize that uncontrolled comorbidities, as well as combination of concomitant diseases, may increase the risk of infection and severity of COVID-19, but this has to be examined.

## 4 | RAAS INHIBITORS AND COVID-19

There are many controversies about the effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) in COVID-19 patients.<sup>24</sup> Some authors expressed their concern that the use of renin-angiotensin-aldosterone system (RAAS) inhibitors and variation in ACE2 expression may be partly responsible for SARS-CoV-2 virulence.<sup>25,26</sup> Population-based studies estimated that only small proportion of hypertensive patients in China (30 to 40%) is treated with antihypertensive therapy, and RAAS inhibitors are used in only 25 to 30% of treated patients.<sup>27,28</sup> Therefore, it can be anticipated that only small percentage of COVID-19 patients in China were actually treated with ACEI or ARB.

**TABLE 1** Demographic parameters and comorbidities in COVID-19 patients

Reference	Sample size	Age <sup>a</sup>	Women (%)	Hypertension (%)	Diabetes (%)	CVD (%)	COPD (%)	Other important findings
Guan et al <sup>3</sup>	1099	47 (35-58)	459 (42)	165 (15)	81 (7)	42 (4)	12 (1)	Epidemiological study, which did not concern the effect of hypertension or CVD on outcome.
Lian et al <sup>4</sup>	788	46	381 (48)	126 (16)	57 (7)	11 (1)	3 (0.4)	Older COVID-19 patients showed significantly higher female gender, rate of comorbidities and rate of severe/critical disease.
Shi et al <sup>5</sup>	416	64 (21-95)	211 (50)	127 (31)	60 (14)	83 (20)	12 (3)	Cardiac injury is common (19.7%) in patients with COVID-19.
Guo et al <sup>6</sup>	187	58.5 ± 14.7	96 (51)	61 (33)	28 (15)	29 (16)	4 (2)	Myocardial injury is significantly associated with fatal outcome of COVID-19. The prognosis of patients with underlying CVD without myocardial injury is significantly better.
Chen et al <sup>7</sup>	274	62 (44-70)	103 (38)	93 (34)	47 (17)	28 (10)	18 (7)	Acute respiratory distress syndrome and respiratory failure, sepsis, acute cardiac injury, and heart failure were the most common critical complications during exacerbation of COVID-19.
Yang et al <sup>8</sup>	52	59.7 ± 13.3	17 (33)	No data	9 (17)	12 (23)	4 (8)	Patients older than 65 years with comorbidities and ARDS had worse clinical outcome.
Zhou et al <sup>9</sup>	191	56 (46-67)	72 (38)	58 (30)	36 (19)	15 (8)	6 (3)	Older age, higher sequential organ failure assessment and D-dimer were predictors of mortality in COVID-19 patients.
Huang et al <sup>11</sup>	41	49 (41-58)	11 (27)	6 (15)	8 (20)	6 (15)	1 (2)	Epidemiological study, which did not investigate the effect of hypertension or CVD.

(Continues)

TABLE 1 (Continued)

Reference	Sample size	Age <sup>a</sup>	Women (%)	Hypertension (%)	Diabetes (%)	CVD (%)	COPD (%)	Other important findings
Guan et al <sup>12</sup>	1590	48.9 ± 16.3	674 (43)	269 (17)	130 (8)	854 (54)	24 (1.5)	COPD, diabetes, hypertension, and malignancy were predictors for admission to intensive care unit, invasive ventilation, and mortality. The risk increased with higher number of comorbidities.
Wang et al <sup>13</sup>	138	56 (22-92)	63 (46)	43 (31)	14 (10)	27 (20)	4 (3)	Study did not investigate the effect of hypertension or CVD.
Liu et al <sup>15</sup>	137	57 (20-83)	76 (56)	13 (10)	14 (10)	10 (7)	2 (2)	Epidemiological study, which did not investigate the effect of hypertension or CVD.
Wu et al <sup>16</sup>	201	51 (43-60)	73 (36)	39 (19)	22 (11)	8 (4)	5 (3)	Older age was associated with ARDS and lethal outcome.
Li et al <sup>17b</sup>	1527	No data	No data	261 (17)	148 (10)	250 (16)	No data	Hypertension, CVD, and diabetes are the most prevalent comorbidities in COVID-19 patients.
Rodriguez-Morales et al <sup>23b</sup>	656	52	289 (44)	122 (18.6)	94 (14.4)	78 (11.9)	No data	36.8% of patients had 1 or more comorbidities. The most significant were hypertension, cardiovascular disease, and diabetes.

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease (coronary heart disease, heart failure, cerebrovascular disease).

<sup>a</sup>Mean, range, average ± standard deviation (depending on published data).

<sup>b</sup>Meta-analysis.

On the other hand, the prevalence of cardiac damage in COVID-19 patients is not negligible, and it is associated with adverse outcome in these subjects.<sup>5,6</sup> Data regarding the frequency of heart failure in COVID-19 patients are scarce, and the same is valid for chronic kidney disease. From therapeutic point of view, ACEI and ARB have important roles in treatment of these conditions—cardiac injury, heart failure, and renal impairment (particularly with albuminuria). Therefore, withdrawing RAAS inhibitors or switching medications would have uncertain benefits, but very certain disadvantages.

It would be expected that problem with RAAS inhibitors would escalate in Western countries (Europe and USA), where patients

are taking antihypertensive medications, and particularly RAAS inhibitors, in significantly higher percentage than in China. However, studies from Italy and USA did not show any association between RAAS inhibitors and susceptibility to coronavirus, complications or mortality from COVID-19.<sup>29-31</sup> Even new investigation from China confirmed these findings.<sup>32</sup> The switching from the RAAS inhibitors to another antihypertensive therapy would lead to insufficient blood pressure control, which could induce more complications in COVID-19 patients than infection of SARS-CoV-2 itself. Novel data showed that RAAS inhibitors could even improve the outcome of hypertensive patients with COVID-19.<sup>33</sup> The authors hypothesized that RAAS

inhibitors have an indirect antiviral role by regulating immune function and inhibiting inflammatory responses.<sup>31</sup> Based on the available data, despite some theoretical possibilities, multiple specialty societies recommended that COVID-19 patients should continue therapy with RAAS inhibitors.<sup>34-36</sup>

## 5 | HYPERTENSION AND OUTCOME IN PATIENTS WITH COVID-19

Limited number of studies provided outcome data after a short follow-up. Therefore, one should be careful in interpretation of these findings. Guan et al demonstrated that patients with severe COVID-19 and those with primary end point (admission in intensive care unit, the use of mechanical ventilation, or death) had significantly higher percentage of hypertension, diabetes, coronary artery disease, cerebrovascular disease, COPD, chronic renal disease, and cancer.<sup>3</sup> The authors did not investigate the relationship between different demographic and clinical parameters with severity of disease or the outcome.

Shi et al reported that hypertension, diabetes, coronary artery disease, cerebrovascular disease, COPD, and cancer were more prevalent in the patients with myocardial injury diagnosed by elevation of high-sensitivity troponin I and creatinine kinase-myocardial band (CK-MB).<sup>5</sup> Cardiac injury was associated with significantly higher mortality (52.1% vs. 4.5%). The authors did not investigate which comorbidities were associated with cardiac injury and mortality. It must be noted that patients with cardiac injury were significantly older. Guo et al demonstrated similar results when compared COVID-19 patients with and without elevation of troponin and found that 27.8% of patients with COVID-19 had cardiac injury.<sup>6</sup> In this study, chronic renal dysfunction and usage of RAAS were also

more prevalent in patients with cardiac injury. However, patients with cardiac injury were almost 20 years older and more frequently men than those without injury, which also have to be taken into account. It was also reported that underlying cardiovascular disease was worsening outcome only in patients with myocardial injury.<sup>6</sup> Defining myocardial injury only by elevation of troponin I in these circumstances could be questionable because this biomarker may be increased in many conditions such as inflammation and/or sepsis/systemic inflammatory response syndrome and kidney injury. The authors did not clearly stated which disorders were included under the term "cardiovascular disease" and it is not clear whether hypertension was included in this term. Furthermore, it is difficult to understand which cardiomyopathies were included and whether patients with heart failure were included.

Chen et al reported that hypertension, cardiovascular disease, and diabetes were more prevalent among COVID-19 patients who died in comparison with survivors.<sup>7</sup> However, there was a large difference in age and sex distribution between groups and authors did not investigate the effect of comorbidities on outcome in this population<sup>7</sup> (Table 2). Zhou et al reported that hypertension, diabetes, coronary heart disease, chronic renal disease, and COPD were more frequent among non-survivors than in survivors.<sup>9</sup> The authors found that hypertension, diabetes, and coronary heart disease were predictors of mortality in COVID-19 patients. Nevertheless, none of these comorbidities remained significant predictor of mortality after adjustment for age, sex, and smoking status. These findings confirmed the importance of comprehensive risk assessment by including all relevant risk factors and comorbidities.

In the large original study that included 1590 patients, Guan et al showed that after adjusting for age and smoking status, patients with COPD, diabetes, hypertension, and malignancy were more likely to reach the composite end points (admission to

**TABLE 2** Demographic parameters and comorbidities of COVID-19 patients in studies that investigated fatal outcome

Reference	Non-survivors/ survivors	Number of patients	Age <sup>a</sup>	Women (%)	Hypertension (%)	Diabetes (%)	CVD (%)	COPD (%)
Chen et al <sup>7</sup>	Non-survivors	113	68 (62-77)	30 (27)	54 (48)	24 (21)	20 (18)	1 (1)
	Survivors	161	51 (37-66)	73 (45)	39 (24)	23 (14)	7 (4)	0
Yang et al <sup>8</sup>	Non-survivors	32	64.6 ± 11.2	11 (34)	No data	7 (22)	10 (31)	2 (6)
	Survivors	20	51.9 ± 12.9	6 (30)	No data	2 (10)	2 (10)	2 (10)
Zhou et al <sup>9</sup>	Non-survivors	54	69 (63-76)	16 (30)	58 (30)	17 (31)	13 (24)	4 (7)
	Survivors	137	52 (45-58)	56 (41)	32 (23)	19 (14)	2 (1)	2 (1)
Du et al <sup>10</sup>	Non-survivors	85	65.8 ± 14.2	23 (27)	32 (38)	19 (22)	17 (20)	2 (2)
Deng et al <sup>14</sup>	Non-survivors	109	69 (62-74)	36 (33)	40 (37)	17 (16)	13 (12)	22 (20)
	Survivors	116	40 (33-57)	65 (56)	18 (16)	9 (8)	4 (3)	3 (3)
Wu et al <sup>16</sup>	Non-survivors with ARDS	44	68.5 (59-75)	15 (34)	16 (36)	11 (25)	4 (9)	No data
	Survivors with ARDS	40	50 (40-57)	9 (23)	7 (18)	5 (13)	4 (10)	No data

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease (coronary heart disease, heart failure, cerebrovascular disease).

<sup>a</sup>Mean, range, average ± standard deviation (depending on published data).

intensive care unit, or invasive ventilation, or death) than those without.<sup>12</sup> Malignancy, COPD, hypertension, and diabetes increased the risk of adverse outcome for 3.5-, 2.7-, 1.57-, and 1.58-fold, respectively.<sup>12</sup> Patients with two or more comorbidities had significantly higher risk of the composite end point than patients with a single comorbidity. Stratification of patients according to their age (<65 years vs ≥65 years) did not show significant difference in the strength of associations between the number of comorbidities and mortality of COVID-19.<sup>12</sup> However, it cannot be excluded that other confounding factors, besides aging and smoking, might also be responsible for the association between comorbidities and outcome. It would be also helpful to divide primary outcome into two separate outcomes: (a) admission to intensive care unit and/or invasive ventilation and (b) death. This would provide separated information about independent predictors of severity and mortality of COVID-19. This was performed in the small study, and authors found that hypertension and diabetes were predictors of acute respiratory distress syndrome, but not mortality in COVID-19 patients.<sup>16</sup> Unfortunately, multivariable analysis with adjustment for relevant confounding factors was not performed in this investigation.

There are a number of limitations in the mentioned investigations. The self-reporting of comorbidities on hospital admission represents one of them. Under-reporting of comorbidities, due to the lack of awareness and/or the lack of diagnostic testing, could interfere the associations between comorbidities and clinical outcome. More importantly, the duration of follow-up was short and some patients remained in the hospital at the time of publishing these studies, which means that real outcome was unknown. Obesity was not reported in available studies, and its influence could not be investigated. Furthermore, only one study reported basal values of systolic and diastolic blood pressure, which would help to estimate the percentage of uncontrolled hypertension. The same refers to prevalence of patients with uncontrolled diabetes. The most of studies included small number of patients, which is additional obstacle. One should not forget the fact that majority of studies come from China, and we should be cautious when extrapolating these findings to other countries with outbreak of COVID-19. Studies should consider all potential sources of bias and confounding, which is why additional investigations with improved design are warranted.

## 6 | CONCLUSIONS

Recent findings reported that arterial hypertension represented one of the most common comorbidities in patients with COVID-19. This prevalence ranged between 10% and 34%. The impact of hypertension on outcome and particularly on mortality in COVID-19 patients is not clear due to lack of data. Studies did not provide evidence that RAAS inhibitors should be avoided or switched in these patients. Large studies that will consider all potential sources of bias and confounding factors, as well as longer follow-up, are necessary.

The public pressure to find all answers is very high, but physicians' duty is to stay rational and has scientific approach to available and upcoming data.

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