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Cardiovascular issue: Hypertension and COVID-19

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Abstract
Coronavirus disease 2019 (COVID-19), caused by a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic that has affected the lives of billions of individuals. Coronavirus disease 2019 (COVID-19) emerged in December 2019 likely as a result of zoonotic transmission from wild animals linked to a large wet market in Wuhan, China.Hypertention as a risk factor in COVID-19 patients explore through various studies reviewed and through these observations find the link between hypertension and COVID-19. Severity of COVID-19 illness is skewed towards the elderly population who have a higher prevalence of hypertension.However, there are number of factors that could potentially confound a possible relationship between hypertension and severe COVID-19. The first is age: both severe COVID-19 and hypertension are common in the elderly.A biomarker is defined as a "characteristic that can be objectively measured and evaluated as an indicator of normal biological and pathological processes, or pharmacological responses to a therapeutic intervention". Biomarkers in COVID 19 can be useful. Patients with hypertension, especially older individuals and those with other known risk factors, are at increased risk of developing severe symptoms during COVID-19 infection. Antihypertensive therapy with ACE inhibitors or ARBs in patients with COVID-19 should be carefully continued, with careful monitoring to detect hypotension and kidney injury. For non-hospitalized patients with COVID-19, ongoing management of comorbid conditions is essential to minimize risk. This includes lifestyle factors such as diet and sleep, along with maintaining regular medications like antihypertensive drugs. Arrhythmias and sudden cardiac arrest are common manifestations of COVID-19. Heart palpitations have been reported to be the main presenting symptom of COVID-19 in patients without a fever or cough. Overall, multidisciplinary management of COVID-19 based on a rapidly growing body of evidence will help ensure the best possible outcomes for patients, including those with risk factors such as hypertension.
Key words: Hypertension, risk factors, Biomarkers, Heart Failure, comorbidities

Introduction

Coronavirus disease 2019 (COVID-19), caused by a strain of coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic that has affected the lives of billions of individuals. Coronavirus disease 2019 (COVID-19) emerged in December 2019 likely as a result of zoonotic transmission from wild animals linked to a large wet market in Wuhan, China.[1] The responsible virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that belongs to the same family as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in late December 2019. Since then, COVID-19 has spread rapidly worldwide and has become a global pandemic affecting >200 countries and territories, with an unprecedented effect not only on public health, but also social and economic activities. Due to its high transmissibility, COVID-19 spread quickly and escalated into a global pandemic. As of June 18, 2020 there were over 8 million documented cases and 450,000 deaths worldwide, including more than 2 million cases and 118,000 deaths in the United States (US).[2]

Early reports from major COVID-19 epicenters including Wuhan and Lombardy, Italy revealed higher morbidity and mortality rates among patients with a history of hypertension, coronary artery disease, diabetes mellitus, chronic kidney disease, and obesity. Since SARS-CoV-2 infects human cells via the angiotensin-converting enzyme II (ACE2) receptor that acts on the renin-angiotensin-aldosterone system (RAAS), a key regular of blood pressure, questions have been raised about a possible link between hypertension and severe COVID-19 infection. This paper will explore the current state of our understanding of this association and review recently published studies evaluating outcomes of hypertension and COVID-19.

Link between Hypertension and COVID-19:

Hypertension, defined by the American College of Cardiology (ACC) and American Heart Association (AHA) as a systolic blood pressure (BP) ≥130 or diastolic BP ≥80 mm[3], is a primary modifiable risk factor associated with atherosclerotic cardiovascular disease.[3] The prevalence of hypertension in US adults is around 50% and higher rates correlate directly with advancing age.[3] According to the Centers for Disease Control (CDC), 63% of adults over the age of 60 are hypertensive,[4] a number that will continue to rise as our population ages. Approximately 50% of US patients with hypertension are prescribed angiotensin converting enzyme inhibitors (ACE-I), aldosterone receptor blockers (ARB) and aldosterone antagonists, collectively called RAAS inhibitors, and are among the most frequently prescribed anti-hypertensive medications.[5]

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Initial reports from COVID-19 hot spots, including Wuhan,[6,7] Lombardy,[8,9] and New York City,[10] identified higher rates of hypertension among severely ill, hospitalized COVID-19 patients. A large US study of 5,700 hospitalized patients revealed an overall hypertension rate of 56%,[10] similar to hypertension rates reported from China[11] and Italy[9] (50% and 49%, respectively). Despite these observations, the link between hypertension and COVID-19 is unclear. Severity of COVID-19 illness is skewed towards the elderly population who have a higher prevalence of hypertension. The median age of hospitalized patients in Lombardy and New York City was 63 years old[9,10] and the percentage with a hypertension diagnosis is consistent with the percentage observed in the general population. While there is an overrepresentation of hypertension among hospitalized and critically ill COVID-19 patients, it is uncertain whether this relationship is causal or confounded by age and other co-morbidities associated with hypertension including obesity, diabetes mellitus, and chronic kidney disease.

Hypertension is very common, affecting an estimated 1.39 billion individuals worldwide, and the prevalence of hypertension increases with age (affecting approximately 70% of older adults). In addition, RAS inhibitors such as ACE inhibitors and ARBs are recommended and widely used for the treatment of hypertension.[11] However, hypertension is not a single clinical entity, but it instead manifests as a number of different phenotypes. In Asians, the disease is characterized by salt sensitivity, high rates of masked hypertension, exaggerated morning BP surge, and nocturnal hypertension. Nearly half of all patients with hypertension worldwide (44%) live in south or east Asia.[12]

Hypertension: As Risk factor in COVID -19

On March 20, 2020, the Italian Institute of Health announced that there had been 3200 COVID-19 deaths in Italy. The patients who died had an average age of 78.5 years (median 80 years, range 31-103 years) and 98.7% had at least one comorbidity. Hypertension was a common comorbidity in Italian cases, affecting 73.8% of patients, 52% of whom were taking ARBs or ACE inhibitors.[13] However, there are number of factors that could potentially confound a possible relationship between hypertension and severe COVID-19. The first is age: both severe COVID-19 and hypertension are common in the elderly. In addition, the identified risk factors are generally associated with aging and/or vascular disorders, both of which are common in patients with hypertension.[Table -1] Therefore, the risk of developing severe COVID-19 is more likely to be due to underlying vascular endothelial dysfunction and/or organ damage than high blood pressure (BP) per se. ACE2 receptors are expressed by endothelial cells, and post-mortem examinations have detected the presence of viral infection in endothelial cells.[14]

Table 1. Risk factors for progression/severity of COVID-19

S.No.	Risk Factors
1	Aging
2	Hypertension
3	Diabetes Mellitus
4	Smoking
5	Cardiovascular disease(heart failure, stroke, angina, myocardial infarction)
6	Chronic Obstructive Pulmonary Disease
7	Chronic kidney diseases
8	Malignancy (especially receiving current treatment with chemotherapy or radiotherapy)

Potential drug–disease interactions

The potential drug–disease interactions in patients with COVID-19 have become a highly researched topic. First, whether antihypertensive agents such as ACE inhibitors and angiotensin II receptor blockers (ARBs) are involved in the progression or prevention of COVID-19 is unknown.[15,16] Second, some of the potential antiviral drugs used to treat patients with COVID-19 are known to induce cardiotoxicity.[17]

Is it safe to continue treatment with ACE inhibitors or ARBs?

Reynolds et al looked at history of antihypertensive usage in 12 594 patients undergoing COVID-19 testing in New York, USA. They did not find any association between the use of ACE inhibitors, ARBs, beta-blockers, calcium channel blockers or thiazide diuretics and the likelihood of a positive or negative result on COVID-19 testing.[18] Also in the United States, Mehta and colleagues failed to find any significant association between the use of ACE inhibitors or ARBs and COVID-19 test positivity.[19] Similar findings were reported in a population case-control study from Italy.[20]

Data from four studies published by early May 2020 also failed to find a significant association between RAS inhibitor use and worse outcomes in patients with COVID-19. In one retrospective case series, the proportion of patients using ACE inhibitors or ARBs did not differ significantly between those with severe vs non-severe COVID-19, or between survivors and non-survivors.[21] However, the in-hospital COVID-19 mortality rate was higher in patients with vs without hypertension (21% vs 11%).[21] In the other studies, death rates for patients taking ACE inhibitors and/or ARBs were actually lower than those in patients not receiving these antihypertensive therapies.[22] One of the studies from China reported that levels of the inflammatory markers

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high sensitivity C-reactive protein and procalcitonin were significantly lower in patients with hypertension who were vs were not receiving ACE inhibitors or ARBs.[23]

Potential Role of Biomarkers in COVID-19

A biomarker is defined as a "characteristic that can be objectively measured and evaluated as an indicator of normal biological and pathological processes, or pharmacological responses to a therapeutic intervention". Biomarkers in COVID 19 can be useful in the following areas. [Table -2]

Table 2: Potential Role of Biomarkers in COVID-19

S.No.	Role of Biomarkers.
1	Early suspicion of disease.
2	Confirmation and classification of disease severity.
3	Framing hospital admission criteria.
4	Identification of high risk cohort.
5	Framing ICU admission criteria.
6	Rationalizing therapies.
7	Assessing response to therapies.
8	Predicting outcome.
9	Framing criteria for discharge from the ICU and/or the hospital.

A strong working knowledge of the pathophysiology is essential for the initial identification of candidate biomarkers, which is, an understanding of what the virus does to the body and how the body reacts to it.

4 BIOMARKERS OF COVID-19-RELATED COMPLICATIONS

Table 3. Biomarkers for progression of COVID-19-related complications

Biomarker	Clinical Condition
Oxygen saturation<94%	Acute respiratory distress syndrome
Troponin	Myocardial injury
D-dimer	Thrombosis
Amino-terminal pro-B-type natriuretic peptide	Heart failure
Creatinine	Kidney injury
C-reactive protein	Cytokine storm
Interleukin-6	Cytokine storm

One of the most important biomarkers in patients with COVID-19 is troponin, which indicates the presence of myocardial injury. D-dimer and IL-6 are also important. D-dimer indicates the presence of arterial microthrombus and venous thrombosis (pulmonary embolism and deep vein thrombosis) and disseminated intravascular coagulation (DIC). IL-6 is an inflammatory marker, suggesting the presence of cytokine storm, while NT-proBNP and creatinine are biomarkers of heart failure and renal damage, respectively.There are two possible mechanisms of cardiovascular damage in COVID-19. The first is direct viral infection of myocardial and vascular cells, and the other is a systemic inflammatory reaction (or cytokine storm) Myocardial injury at the time of admission or due to disease progression is a strong indicator of poor prognosis in patients with COVID-19.A systematic review and meta-analysis of data published between 1 December 2019 and 27 March 2020 including 4189 patients from 28 studies showed a significant trend for higher levels of cardiac biomarkers in patients with more severe COVID-19.[24]D-dimer is a biomarker that reflects activation of coagulation and fibrinolysis.[25] D-dimer levels of >2 µg/mL were an independent predictor of in-hospital death in patients hospitalized with COVID-19 in Wuhan, China (hazard ratio 51.5, 95% CI 12.9-206.7; $P < .001$).[26] The 2 µg/mL cut-off had 92% sensitivity and 83% specificity for predicting in-hospital mortality and therefore might be a useful biomarker for predicting outcome and informing treatment decisions in patients with COVID-19.important screening tool is oxygen saturation, which indicates severe disease if ≤94% on admission.[27]Actually if track data which are available there are number of factors and biomarkers that can be used to identify patients with COVID-19 who are at high risk of more severe disease and adverse outcomes, including death. Age seems to be the most important risk factor, especially for COVID-19-related death, and hypertension is the most common comorbidity in COVID-19-positive deceased patients. Other comorbidities such as cardiovascular diseases, smoking, chronic lung disease, chronic kidney disease, and a suppressed immune system also increase the risks associated with COVID-19 infection, especially when multiple comorbidities exist in the same patient.[28]

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Biochemical Parameters

Serum Albumin

Hypoalbuminemia in critically ill patients is multifactorial and is attributed to increased capillary permeability, decreased protein synthesis, increased turnover, decreased serum albumin total mass, increased volume of distribution, and increased expression of vascular endothelial growth factor.

LDH

About 40% of patients presented with increased LDH levels. Elevated LDH has been associated with a higher risk of ARDS, need for intensive care and mortality

Suggested Assessment and management of COVID-19 Comorbidities

- Patients with hypertension, especially older individuals and those with other known risk factors, are at increased risk of developing severe symptoms during COVID-19 infection.
- High-risk patients, such as those with hypertension, are more likely to develop cardiac injury during COVID-19 infection.
- Diabetes mellitus should be carefully managed and these patients need to be closely monitored for the development of myocardial injury and arteriovenous thrombosis.
- Consider determining levels of key biomarkers, especially troponin and D-dimer, to get a complete clinical picture and information about prognosis in patients with COVID-19.
- Oxygen saturation should be determined at presentation; if oxygen saturation is <94% then COVID-19 should be considered as severe.
- COVID-19 progression and cardiovascular status can be monitored by measuring blood pressure and taking the patient's temperature.
- Antihypertensive therapy with ACE inhibitors or ARBs in patients with COVID-19 should be carefully continued, with careful monitoring to detect hypotension and kidney injury.
- Unmedicated older COVID-19 patients whose only comorbidity is hypertension can be treated with calcium channel blockers.
- Physicians should be aware of physical manifestations of stress (e.g., cardiovascular events), even in individuals not infected with COVID-19 (especially those with pre-existing hypertension).

For non-hospitalized patients with COVID-19, ongoing management of comorbid conditions is essential to minimize risk. This includes lifestyle factors such as diet and sleep, along with maintaining regular medications (eg, antihypertensives and antidiabetics). Patients with hypertension on current therapy with ACE inhibitors or ARBs can continue treatment without any negative effects on COVID-19 outcomes. For older patients with hypertension and no other comorbidities and risk factors, calcium channel antagonists might be a good option for antihypertensive therapy.In addition, regular monitoring of home BP will help to ensure the achievement and maintenance of BP targets in patients with hypertension.Lockdown requirements could impact on the ability of individuals to get regular exercise. Regular exercise is important for maintaining health status and to counteract the negative consequences of cardiovascular, metabolic, and respiratory diseases.[29] Even if unable to get outside, continuing some form of home-based exercise would be beneficial, especially in older adults.[30] In another study in Wuhan involving 187 patients hospitalized with COVID-19, those with elevated levels of troponin T were more likely to develop malignant arrhythmias, such as ventricular tachycardia and fibrillation, than those with normal levels of troponin T (12% versus 5%).[31]

Heart failure in COV9ID -19

In an early study from Wuhan involving 799 patients, heart failure was one of the most commonly observed complications of COVID-19, with a reported incidence of 24% in all patients and 49% in patients who died76. Elevated levels of amino-terminal pro-B-type natriuretic peptide were identified in 49% of all patients (85% of those who died).Similarly, in another study of 191 patients in Wuhan, heart failure was identified in 23% of all patients and in 52% of patients who died.[32] Given that COVID-19 primarily causes respiratory symptoms and viral pneumonia with bilateral, peripheral and lower lung distribution, the pulmonary oedema that is observed in these patients, which is usually accompanied by ARDS, is mainly regarded as non-cardiogenic. However, given that approximately 25% of patients hospitalized with COVID-19 develop heart failure, the potential contribution of pulmonary congestion by heart failure should be taken into consideration.[33]

Arrhythmias and sudden cardiac arrest. Arrhythmias and sudden cardiac arrest are common manifestations of COVID-19. Heart palpitations have been reported to be the main presenting symptom of COVID-19 in patients without a fever or cough.[34] In a cohort of 138 patients with COVID-19 in Wuhan, China, the presence of cardiac arrhythmia was reported in 17% of all patients (44% of patients in the ICU), but the specific types of arrhythmia were not recorded.[35]

Cardiovascular effects of antiviral drugs at present, many research teams worldwide are focused on the development of drugs for the prevention and treatment of COVID-19.[36] Of note, the development and testing of new drugs are time-consuming processes139 and not a viable strategy during this COVID-19 pandemic. Drug repurposing, in which existing medications that have already been approved for a disease are tested for a new condition, is currently the main approach in the search for new drugs for COVID-19. However, some of the

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drugs under investigation have known or unknown cardiovascular adverse effects or might be involved in drug–drug or drug–disease interactions.[37,38]

General Recommendations FOR COVID -19

Based on the currently available evidence, summarized as above we would like to offer the following recommendations with respect to the use of biomarkers in adults. These are primarily based on the clinical categorization as per the WHO guidelines, but should be modified according to the clinical condition, presence of comorbidities, availability and cost.

• For patients who are asymptomatic or in the mild category (without underlying comorbidity), no investigations are needed.

• For all patients in the mild category with associated comorbidity or patients in the moderate category, a complete blood count (CBC), CRP, serum creatinine, and liver function tests are needed at admission. If any of these markers are abnormal, further investigations mentioned for patients in the severe category may be considered. If symptoms persist in the second week, CBC and CRP must be repeated to see the trends to decide monitoring and further investigations.

• For all patients in the severe category, in addition to the markers mentioned above, PT, APTT, INR, serum ferritin, d-dimer and cardiac biomarkers (NT-pro-BNP and troponin I) are advisable.

• Patients in the critical category, would need, in addition to the markers mentioned in the above categories, serum IL-6 levels and serial lactate levels.

• To monitor hospitalized patients on therapy, CBC and CRP should be repeated 48 to 72 h after admission or earlier. Serum ferritin cannot be recommended to monitor response to therapy based on current evidence.

CONCLUSIONS

COVID-19 is a heterogeneous disease spectrum with manifestations varying with age and presence of co-morbidities. Biomarkers will play a crucial role in early suspicion, diagnosis, monitoring, and recognition of complications, management and disposition of patients. Each of these components in turn can have crucial implications on the healthcare system and the administrative machinery, directly impacting patient care. Needless to say, clinical evaluation will be paramount at every step and biomarkers will need to be meaningfully integrated into bedside decision making. Patients with hypertension are at increased risk of morbidity and mortality if they become infected with SARS-CoV-2, although this is confounded by other factors such as age and vascular disorders. However, all usual antihypertensive therapy including RAS inhibitors should continue. Physicians need to take a holistic approach to patient management due the wide range of possible complications, and biomarkers can provide important prognostic information. Overall, multidisciplinary management of COVID-19 based on a rapidly growing body of evidence will help ensure the best possible outcomes for patients, including those with risk factors such as hypertension.The COVID-19 pandemic is changing our lives in unprecedented ways.The capacity of health-care systems globally has been severely tested (and in some countries completely overwhelmed), and the effect of this pandemic on social interactions, health-care delivery and the global economy continues to mount. Reduced physical activity owing to lockdown measures might also contribute to poor control of cardiovascular risk factors.To meet the urgent need for effective treatment and preventative strategies, a concerted effort must be made by researchers globally to investigate and integrate biological and clinical findings related to COVID-19.

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