



# COVID19 and increased mortality in African Americans: socioeconomic differences or does the renin angiotensin system also contribute?

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## Introduction

The dawn of the new decade is marked by the emergence of the novel coronavirus SARS-CoV-2, whose spread has resulted in the COVID-19 pandemic, having already affected millions of individuals and resulted in hundreds of thousands of deaths worldwide [1, 2]. While the pandemic situation is constantly evolving, alarming signals have arisen during the past few weeks from the United States of America, which now represents the world's most affected country, as disproportionately higher infection and mortality rates in African-Americans compared to other races were reported in some states [3, 4]. After these initial reports that raised public awareness, most states gradually started sharing data regarding confirmed cases and deaths by race. Most of them have reported higher infection rates in African-Americans, although data regarding confirmed COVID-19 cases by race are largely incomplete [5]. Furthermore, based on current estimates, it is calculated that overall African-Americans suffer from a 2.4 and 2.2 times higher mortality rate when compared to Whites and Asians or Latinos, respectively [6, 7].

The first thing that needs to be addressed is whether this phenomenon is actual or COVID-19 was spread in states with a relatively higher African-American population. Available data suggest that the mortality rate is indeed higher, even when adjusted for the African-American population in each state in most cases. In Illinois, for instance, 14% of the population which is African-Americans accounts for 36% of confirmed COVID-19 deaths. Similarly,

in Michigan 43% of deaths concerned African-Americans who represent 14% of the state's population [7]. However, more data is eagerly needed on this topic: first of all from every state, and second for specific counties as well, since the population is not evenly divided by race within each state.

The higher mortality rate in African-Americans raises questions about the underlying mechanisms behind these racial disparities. Several known mechanisms might be implicated, including increased comorbidities, inequalities in healthcare access, and socioeconomic factors. However, we propose that another mechanism might be also implicated: the renin-angiotensin system.

## Comorbidities

Cumulative evidence from China and Italy, two countries being at the epicenter of COVID-19 pandemic before the US, suggests that, besides age, comorbidities such as cardiovascular disease (mainly ischemic heart disease and stroke), hypertension, diabetes mellitus, chronic respiratory disease and atrial fibrillation increase the risk of mortality among the affected patients [8, 9]. Indeed, hypertension increases the risk for the development of acute respiratory distress syndrome (ARDS) by 82%, while diabetes mellitus augments the corresponding risk by 134% [10]. Hypertension is more prevalent among African-Americans, even at earlier ages, compared to other races, while control rates remain poorer [11, 12]. Besides, it has been previously demonstrated that black patients with diabetes mellitus feature significantly greater odds for insufficient glycemic control, compared to nonHispanic whites [13], while they also have a significantly higher rate of in-hospital complications, compared to nondiabetic white patients with hyperglycemia. However, no statistically significant difference for adverse in-hospital outcomes is observed, when

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white and black patients with diabetes are compared [14]. Of note, African-American women have been shown to have a greater risk for stroke, heart failure and end-stage renal disease (ESRD) compared to white women, whereas African-American men feature greater risk for heart failure and ESRD, but lower risk for coronary artery disease compared to white men [15]. Collectively, that evidence might partially explain the greater burden of COVID-19 pandemic among black patients.

## Socioeconomic factors and healthcare access

Socioeconomic factors could also play a significant role. While billions of people worldwide are encouraged to implement teleworking, for many African-Americans it is not a matter of choice due to working in essential industries, with less than 20% being able to work from home, rising the possibilities for exposure and infection [16]. Social distancing has been so far recognized as the most effective measure of spread attenuation [17]. However, the family structure differs in African-Americans, as family members share closer bonds and are more likely to share accommodation, resulting in close contact among the elderly and the youth, who are also more unlikely to conform to social distancing. In fact, the spread of the disease in China and Europe during the previous months led several people to assume that African-Americans are “immune” to COVID-19, resulting in significant misinformation on this issue with obvious consequences. Indeed, a recent report revealed that many African-Americans lack critical knowledge about COVID-19 and have not changed their daily routine [18].

Given that the unemployment and uninsurance rates for African-Americans are higher than average, their access to healthcare facilities is significantly disabling and probably resulting in under detection of less serious cases [19]. Another significant factor in this field is the relatively higher mistrust of African-Americans in the healthcare system [20]. The limited access to combined with the mistrust at the healthcare system might result in significant delays in seeking assistance, and thus increased mortality rates in African-Americans.

However, Latinos share some of the above-mentioned socioeconomic characteristics, at least partly, although early reports suggest that they exhibit lower mortality rates compared to African-Americans, as it has already been mentioned [7].

## Renin-angiotensin system

We should also highlight the potential role of renin-angiotensin-aldosterone system (RAAS) blockers use

among black patients. Low plasma renin activity, associated with a salt-sensitive phenotype, has been documented for black patients compared to white individuals [21]. The hallmark ALLHAT trial, which enrolled a significant proportion of black patients, demonstrated for the first time the superiority of chlorthalidone compared to lisinopril in the prevention of surrogate endpoints, namely stroke, combined coronary artery disease and cardiovascular disease and heart failure [22]. Thus, according to the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines, initial antihypertensive treatment in black adults with hypertension but without heart failure or chronic kidney disease, including those with diabetes mellitus, should include a thiazide-type diuretic or a calcium-channel blocker (CCB) [23]. However, a recent meta-analysis pooling data from a total of 38,983 hypertensive black patients did not reveal a significant difference between RAAS blockers and the rest antihypertensive drug classes regarding the odds for hard endpoints, except for stroke; patients treated with RAAS blockers featured an over 50% increase in the odds for stroke, compared to those treated with diuretics or CCBs [24]. Anyway, the fact is that the use of RAAS inhibitors is less common in African-Americans compared to Caucasians [25].

Based on the pathophysiologic background underlying SARS-CoV-2 infection, several preclinical studies raised concerns on the safety of RAAS blockers in patients with documented infection; however, there is no hard evidence to support the discontinuation of these agents, especially in high-risk patients [26]. For this reason, several scientific societies, such as the European Societies of Hypertension and Cardiology (ESH, ESC), the Heart Failure Society of America, the American College of Cardiology and the American Heart Association (HFSA/ACC/AHA) issued statements that advised towards the continuation of RAAS blockers for indications that are known to be beneficial [27–29]. Furthermore, recent evidence suggests that their use not only cannot be associated with increased risk of COVID-19 or increased risk of in-hospital mortality, but also it has been associated with improved survival, although with limitations [30–32]. Of note, no differences have been reported among ACE inhibitors and angiotensin receptor blockers regarding major clinical outcomes (severity of SARS-CoV-2 infection, mortality) [33, 34]. Therefore, it has to be elucidated whether the lower usage rates of RAAS blockers among black patients could partially contribute to the observed racial disparity in the severity of SARS-CoV-2 infection.

It has been demonstrated that SARS-CoV-2 invades human alveolar epithelial cells through the angiotensin converting enzyme 2 (ACE2) receptor, leading to downregulation of ACE2 expression and rapid progression to ARDS [35]. It would be therefore interesting to know whether black patients

exhibit greater genetic susceptibility to SARS-CoV-2, even though the genetic basis of ACE2 expression in different populations remains largely unknown [36]. What is more, specific ACE2 gene polymorphisms have been correlated with essential hypertension, atrial fibrillation, major adverse cardiovascular events, reduced left ventricular ejection fraction and increased left ventricular mass, mainly in Asian, and Caucasian populations [37–40]. Therefore, one could speculate that there might be a vicious circle between increased susceptibility to SARS-CoV-2, cardiovascular comorbidities and final development of severe infection, which has to be proven. Unfortunately, there are no data until now regarding the interconnection between ACE2 polymorphisms and cardiovascular disease development in African–American populations. Existing gene databases, such as the Million Veteran Program including over 825,000 Veteran participants, could serve as a valuable tool towards this direction [41].

## Conclusion

Undoubtedly, COVID-19 pandemic will continue to strain health care systems worldwide. As our understanding regarding the pathophysiologic mechanisms implicated in this disease further evolves, we may be able to better acknowledge demographic, genetic, behavioral and health factors that are associated with increased mortality in specific vulnerable groups, such as African–Americans.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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