Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers

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ABSTRACT

Background and aims: COVID-19 is already a pandemic. Emerging data suggest an increased association and a heightened mortality in patients of COVID-19 with comorbidities. We aimed to evaluate the outcome in hypertensive patients with COVID-19 and its relation to the use of renin-angiotensin system blockers (RASB).
Methods: We have systematically searched the medical database up to March 27, 2020 and retrieved all the published articles in English language related to our topic using MeSH key words.
Results: From the pooled data of all ten available Chinese studies (n = 2209) that have reported the characteristics of comorbidities in patients with COVID-19, hypertension was present in nearly 21%, followed by diabetes in nearly 11%, and established cardiovascular disease (CVD) in approximately 7% of patients. Although the emerging data hints to an increase in mortality in COVID-19 patients with known hypertension, diabetes and CVD, it should be noted that it was not adjusted for multiple confounding factors. Harm or benefit in COVID-19 patients receiving RASB has not been typically assessed in these studies yet, although mechanistically and plausibly both, benefit and harm is possible with these agents, given that COVID-19 expresses to tissues through the receptor of angiotensin converting enzyme-2.
Conclusion: Special attention is definitely required in patients with COVID-19 with associated comorbidities including hypertension, diabetes and established CVD. Although the role of RASB has a mechanistic equipoise, patients with COVID-19 should not stop these drugs at this point of time, as recommended by various world organizations and without the advice of health care provider.

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1. Introduction

Coronavirus disease 2019 (COVID-19) has been declared as a pandemic by Word Health Organization on March 11, 2020, as soon as it satisfied the epidemiological criteria (infection in more than 100,000 people in 100 countries) [1]. As of March 27, 2020, world has witnessed more than half a million cases of COVID-19 with more than 24,000 deaths [2]. This suggests the magnitude of its spread across the world, since it was first reported on December 31, 2019 from Wuhan, Hubei province in China. Emerging data suggests that older COVID-19 patients with other comorbid conditions such as diabetes, hypertension, cardiac and pulmonary disease are in particular more susceptible, compared to general populations and have higher mortality. Therefore, it is necessary to re-look into these subgroups of COVID-19 patients with associated comorbidities.

In this review article, we have collated all the available evidence that has emerged so far on outcomes and comorbidities in patients with COVID-19. Here, we have focused on outcomes in patients of COVID-19 with hypertension and analyzed the controversies surrounding the use of renin-angiotensin system blockers (RASB).

2. Methods

We have systematically searched the PubMed medical database up till March 27, 2020 using MeSH key words that include Covid-19, coronavirus, hypertension, diabetes, cardiovascular disease, angiotensin receptor blockers, angiotensin converting enzyme

inhibitors. We have retrieved all the available literature published in English language on COVID-19, that reported the outcomes in different co-morbidities.

3. Results

3.1. Hypertension as a significant comorbidity with COVID-19

The association of hypertension and diabetes in patients with COVID-19 is not unexpected, given the rising prevalence of both of these chronic diseases, globally. Interestingly, in the pooled data from the ten Chinese studies (n = 2209) that have reported the characteristics of comorbidities in patients with COVID-19; associations of hypertension, diabetes and presence of established cardiovascular disease (CVD) are larger, varying from 15 to 30% (average 21%), 5–20% (average 11%) and 2–40% (average 7%) respectively (Table 1). Established CVD was also present in nearly 43% in Italian study of 355 patients with COVID-19. Table summarizes the prevalence of these comorbidities in all available studies to-date in patients with COVID-19 [3–14].

3.2. Hypertension as a prognostic indicator for severity and mortality in COVID-19

While consistent association of hypertension in patients with COVID-19 across all these studies is unique, the concern which needs a serious attention is the increase in mortality. Two Chinese studies have worked in this direction to-date. In 191 patients with COVID-19, Zhou et al. found hypertension to have an odds ratio (OR) of 3.05 (95% CI, 1.57 to 5.92; p < 0.006), diabetes with OR of 2.85 (95% CI, 1.35 to 6.05; p < 0.001), whereas presence of coronary artery disease had an OR of 21.40 (95% CI, 4.64 to 98.76; p < 0.0001) for in-hospital mortality, in an univariate analysis [8]. However, the association between these disorders and COVID-19 mortality were no longer significant after a multivariate regression analysis. Similarly, in an analysis of 201 patients with COVID-19, Wu et al. found hypertension to have a hazard ratio (HR) of 1.82 (95% CI, 1.13 to 2.95; p = 0.01) for acute respiratory distress syndrome (ARDS) and 1.70 (95% CI, 0.92 to 3.14, p = 0.09) for death. The diabetic patients had a HR of 2.34 (95% CI, 1.35 to 4.05; p = 0.002) for ARDS and HR of 1.58 (95% CI, 0.80 to 3.13, p = 0.19) for death, in a bivariate cox regression analysis [11]. It should be noted however, that neither of these studies were adjusted for all confounding variables. Nevertheless, a study of 187 patients with COVID-19, Guo et al. reported nearly a twice increase in mortality in patients with established CVD and raised troponin T (TnT), compared to patients without CVD and raised TnT (69.4% vs. 37.5% respectively) [14].

The Chinese Center for Disease Control and Prevention in a summary report of COVID-19, reported a case fatality rate (CFR) of 2.3% (1023 deaths among 44,672 confirmed cases). However, CFR was elevated to 6.0% for hypertension, 7.3% for diabetes, and 10.5% for presence of CVD [15]. Unsurprisingly, based on the above findings, researchers have recently proposed that the course of treatment and prognosis of COVID-19 should be stratified based on the absence or presence of co-morbidities in to type A, B and C. Type A denotes COVID-19 patients with pneumonia but without comorbidities, Type B denotes COVID-19 pneumonia and comorbidities, whereas, Type C denotes COVID-19 patients with multi-organ dysfunction [16].

Nonetheless, it still remains unclear whether these increased association of hypertension with COVID-19 and heightened risk of mortality is directly related to hypertension or other associated comorbidities, or, anti-hypertensive treatment. There has been a growing concern that this association with hypertension and or CVD may be confounded by the treatment with certain antihypertensive medications such as RASB. Although a recent paper has proposed to stop RASB and suggested to replace it with the calcium channel blocker, while treating hypertension in patients with COVID-19 [17], this hypothesis has been questioned by several other colleagues [18–22].

3.3. Role of renin angiotensin system and its inhibitors in SARS CoV2 infection

The entry of coronavirus into the cell is facilitated by the spike (S) protein. Before attachment to the receptor on host cell, the S protein needs to be primed by a serine protease named TMPRSS2. The S proteins of different coronaviruses may utilise different receptors; MERS utilises CD26 while SARS CoV and SARS CoV2 utilise Angiotensin Converting Enzyme-2 (ACE-2) [23]. The efficiency of the interaction between S-protein and ACE-2 may be a key determinant of the transmissibility of the virus, viral replication and the severity of disease. In theory, this efficiency could be influenced by changes or amino acid substitutions in either the viral S-protein or

Table 1
Hypertension, diabetes and other co-morbidities in COVID-19, world-wide data.

First author	n	Smokers, %	HTN, %	Diabetes, %	CVD, %	COPD, %	CKD, %	CLD, %	Ref.
COVID-19 in China									
Liu et al.	61	6.6	19.7	8.2	1.6	8.2	NR	NR	3
Guan et al.	1099	12.6	15.0	7.4	3.8	1.1	0.7	NR	4
Huang et al.	41	7.3	14.6	19.5	15.0	2.4	NR	2.4	5
Chen et al.	99	NR	NR	12.1	40.0	1.0	NR	NR	6
Wang et al.	138	NR	31.2	10.1	19.6	2.9	2.9	2.9	7
Zhou et al.	191	6.0	30	19	8.0#	3.0	1.0	NR	8
Zhang et al.	140	NR	30	12.1	8.6	1.4	1.4	NR	9
Yang et al.	52	4.0	NR	17.0	23.0	8.0	NR	NR	10
Wu et al.	201	NR	19.4	10.9	4.0	2.5	1.0	3.5	11
Guo et al.	187	9.6	32.6	15.0	11.2#	2.1	3.2	NR	14
Overall, China, *N = 2209*		**10.7%**	**20.7%**	**10.5%**	**7.4%**	**2.0%**	**1.2%**	**3.2%**	
COVID-19 in Italy									
Onder et al.	355	NR	NR	35.5	42.5	NR	NR	NR	12
COVID-19 in Singapore									
Young et al.	18	NR	NR	NR	NR	NR	NR	NR	13

reported coronary heart disease only, HTN- hypertension, CVD- cardiovascular disease, COPD- chronic obstructive pulmonary disease, CKD- chronic kidney disease, CLD- chronic liver disease, NR- not reported, Ref.- references

the ACE-2 receptor on host cell.

a) *Changes in S-protein*: Molecular studies and the elucidation of the atomic and crystal structure of ACE-2/S protein interface of SARS CoV have provided important insights [24]. The major outbreak of SARS CoV occurred in 2002–2003 with a minor localised outbreak with mild symptoms in 2003–2004. It was observed that the S-protein of SARS CoV in the 2002–2003 outbreak bound to ACE-2 receptor much more efficiently than that of SARS CoV in the 2003–2004 outbreak, consistent with the absence of human-to-human transmission during the latter outbreak. Several molecular changes in the S-protein influence the binding with human ACE-2; for example, the substitution of threonine by serine at position 487 in S protein reduces the binding [25]. Similarly, asparagine at position 479 increased the binding affinity [26]. Methylation at position 487 has also been shown to influence binding. Recently, S-protein of SARS CoV2 has been shown to be similar to that of SARS CoV, barring a few gains of function mutations. The most important of these is a glutamine at position 493 at the receptor binding domain, which explains its increased transmissibility compared to SARS CoV [27].

b) *Changes in ACE-2 Receptor*: With regard to MERS-CoV, which employs CD26 (DPP-4) as its receptor for cellular entry, there are naturally-occurring polymorphisms in DPP4 that impact cellular entry of MERS-CoV and might thus modulate MERS development in infected patients [28]. There is a possibility that similar variations or polymorphisms in ACE-2 could affect the viral entry and disease course. Polymorphisms of ACE-2 gene have been identified; however, there is no evidence that they affect susceptibility to or severity of SARS CoV2 infection [29]. A recent study found differential ACE-2 gene expression in human lung tissue with no racial/gender differences, but a higher gene expression in lungs of smokers compared to non-smokers, which could explain the higher risk of infection in smokers [30].

3.4. Physiological role of ACE-2 and its relationship with coronavirus infection

The role of ACE-2 on vascular bed is opposite to that of angiotensin converting enzyme (ACE). ACE converts angiotensin I to angiotensin II, which is a vasoconstrictor. ACE-2 converts angiotensin II to angiotensin (1–7) which causes vasodilatation after binding to the Mas receptor in the vascular bed [31]. Down-regulation of ACE-2 was observed in animal models of lung injury induced by SARS CoV [32]. Recombinant ACE-2 improved pulmonary blood flow and oxygenation in animals with lung injury, indicating that ACE-2 may be the main determinant of lung injury caused by SARS CoV [33]. However, there is lack of human data except a small study in 10 patients with acute respiratory distress syndrome which showed that recombinant ACE-2 was well tolerated and led to an increase in angiotensin (1–7) [34].

3.5. Effects of ACE inhibitors and angiotensin receptor blockers

There has been much interest regarding the role of RAS blockers in COVID-19 infection. Both benefit and harm have been postulated. Figure 1 illustrates the interactions between the effect of RASB and COVID-19. Fig. 1

a) *Rationale and Evidence for Harm*: There is evidence that ACE-2 expression increases with the use of ACE inhibitors and ARB, especially in heart and kidney [35,36]. This has raised a theoretical concern that by increasing ACE-2 expression, ACEIs and ARBs could facilitate the entry of virus into the
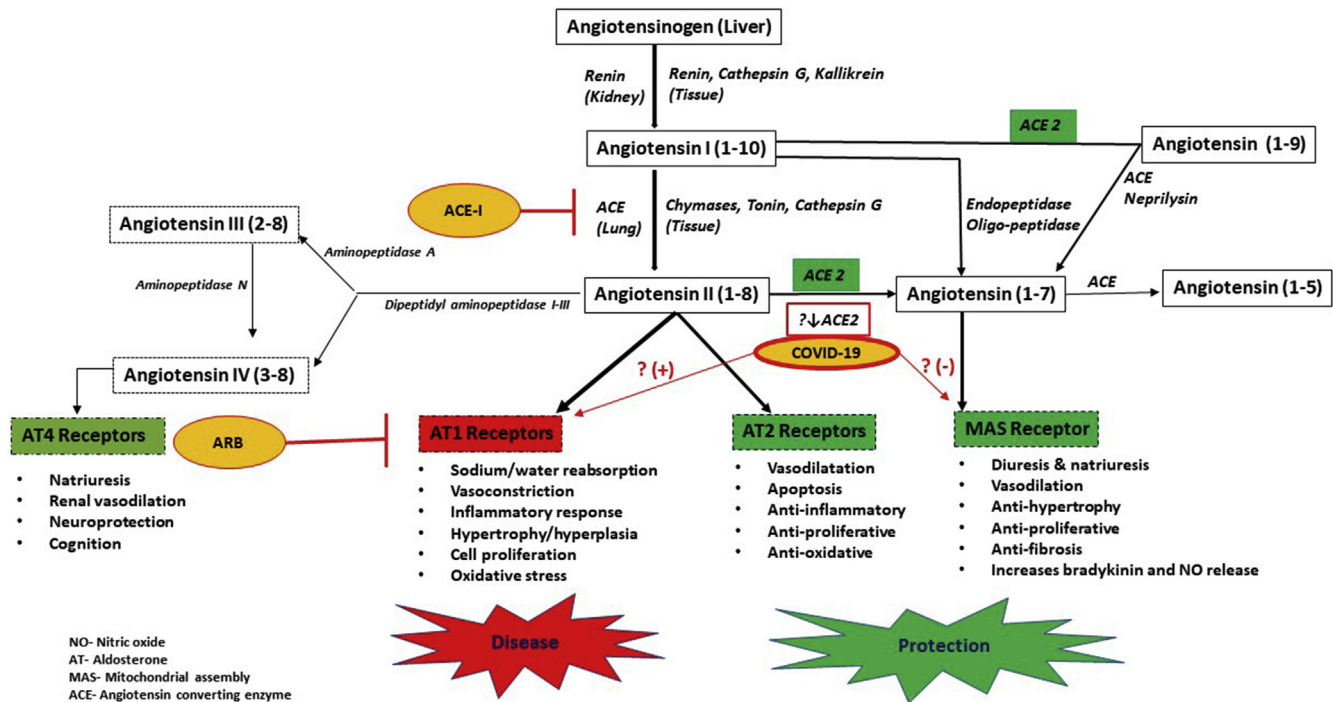

Figure: Components of Renin-Angiotensin System pathway and possible interaction of Angiotensin Converting Enzyme inhibitors (ACE-I), Angiotensin-Receptor Blockers (ARB) and COVID-19

Fig. 1. Components of Renin-Angiotensin System pathway and possible interaction of Angiotensin Converting Enzyme inhibitors (ACE-I), Angiotensin-Receptor Blockers (ARB) and COVID-19.

host cell and increase the chances of infection or its severity [17]. Also, there is increased ACE-2 expression in elderly [37]. To what extent this predisposes the elderly to infection with SARSCoV2 is not known. In a study of 187 patients with COVID-19, Guo et al. reported an increased trend in mortality with those receiving RASB, compared to those not receiving. Mortality was 36.8% (6 of 19) and 25.6% (43 of 168) in patients with or without RASB, respectively [14]. Indeed, increased association and heightened mortality with COVID-19 have been observed consistently across the studies in elderly, hypertensive, diabetics and known CVD; however, it is not exactly known whether it has any causal relation with the use of RASB or these subgroups are more on RASB due to these illness, compared to the rest of population. Moreover, there is no solid evidence to back this concern either in COVID-19 or in infection by other coronaviruses.

b) *Rationale and Evidence for Benefit*: As discussed above, increasing ACE-2 levels in coronavirus infection could reduce lung injury. In an experimental study with mice, Kuba et al. found that losartan showed significantly diminished lung injury and pulmonary edema after acid aspiration-induced acute lung injury (with addition of SARS-CoV spike protein) compared to placebo [32]. Similarly, severe lung injury and pulmonary edema were prevented by both recombinant human ACE-2 infusions or losartan in ACE2-knockout mice [38]. Mice with coronavirus induced lung injury showed improvement when treated with losartan [39]. Moreover, a retrospective analysis found reduced rates of death and endotracheal intubation in patients with viral pneumonia who were continued on ACE inhibitors [40]. Treatment with ARBs was reported to reduce mortality in Ebola virus infection [41]. The exact mechanism of apparent benefit of these drugs in coronavirus infection is not yet clear. However, there could be several explanations [42].

i. Increased ACE-2 expression may not result in more viral entry into the cell because of the limited availability of the serine protease TMPRSS2. Camostat mesylate, which is a TMPRSS2 inhibitor, has been shown to inhibit cellular entry of SARS CoV2 and could be a potential therapeutic option [43].

ii. Increased ACE-2 expression on the cell membrane may also lead to increased soluble ACE-2 in blood, which may actually bind to most of SARS CoV2 and prevent its interaction with the membrane bound receptor.

iii. RAS blockers increase angiotensin II, which is a substrate for ACE-2. The interaction of ACE-2 with angiotensin II could induce a conformational change in the receptor binding domain of ACE-2, limiting its ability to bind with SARS CoV2 [44].

iv. ACE-2 receptors are present at a much higher density in lung tissue of children and young adults, compared to older individuals. Thus, the upregulation of ACE-2 receptors by the use of RASB over time in older people may emulate ACE expression in young people. It is also possible that having more ACE-2 receptors and increased ACE-2 functions will likely produce more angiotensin (1–7) that might provide resilience against target-mediated destruction and development of pulmonary failure in patients with COVID-19 [22]. This postulated positive effects on lung can be also protective during overwhelming infection with COVID-19.

v. Indiscriminate discontinuation of RASB in patients with heart failure may also lead to readmission to hospital and increase in mortality [45].

Collectively, relationship between RAS activity and use of RASB

in SARS CoV2 infection is very scarce. The only indirect evidence of RAS activation in COVID-19 is high incidence of hypokalaemia [46]. With regards to the use of RASB, a retrospective analysis of 112 COVID-19 hospitalised patients with cardiovascular disease in Wuhan, there was no significant difference in the proportion of ACEI/ARB medication between non-survivors and survivors [47]. However, a study of 187 patient reported by Guo et al., there was a trend of increase in mortality in patients with COVID-19 receiving RASB (36.8%), compared to those not receiving (25.6%) [14].

4. Conclusion

COVID-19 is increasingly associated with comorbidities that include hypertension and diabetes. Special care is required in patients with COVID-19 with associated comorbidities, given the heightened risk of in-hospital death.

In view of lack of robust evidence for either benefit or harm, and with bulk of the experimental evidence in favour of benefit, it is reasonable for patients to continue using ACE inhibitors and ARB, as recommended by the European Society of Cardiology, Hypertension Canada, The Canadian Cardiovascular Society, UK Renal Association, the International Society of Hypertension, and European Society of Hypertension and American Heart Association [48–50]. Future studies reporting the outcome stratified on the basis of different anti-hypertensive agents in COVID-19 may further enlighten us in this regard.

Declaration of competing interest

We hereby declare that we have no conflict of interest related to this article.

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