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Delineating clinical characteristics and comorbidities among 206 COVID-19 deceased patients in India: Emerging significance of renin angiotensin system derangement

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ABSTRACT

Aim: While there are rampant deaths reported worldwide due to novel corona virus (COVID-19) on one side, hypertension, diabetes and renal failure are emerging comorbidities with mortality risk due to respiratory failure on the other side. The link of these morbidities with renin angiotensin system (RAS) and angiotensin converting enzyme-2 (ACE2) as the site of the multiplication of COVID-19 has widely been accepted. The objective of this research report was to delineate the clinical characteristics with COVID-19 infection with RAS and to consider its significance not just for the search of novel antiviral drugs, but for the management and prevention of death of patients with COVID-19.

Methods: It was a retrospective case series analysis of demographic and clinical data with associated comorbidities of 206 deaths reported in India up to 10th April 2020. The data were available from the official release from Ministry of Health and Family welfare, Government of India. This was followed by a literature search to correlate the available evidence for their possible relationship with RAS.

Results: The demographic data were consistent with those reported from other countries. The death (53.4%) was more common in patients with age above 60 years and men (69.3%) were more susceptible as compared to women (30.68%).We found that 50.5% of the deceased patients had pre-existing comorbidities. Diabetes and hypertension were the major comorbidities in 27.8% and 22.1% of the deceased cases respectively. Although respiratory and cardiac problems were prevalent at the time of death, the pre-existing pulmonary disease was comparatively less prevalent. Only 13.6% of the deceased were having pre-existing respiratory problems and 6.2% had cardiac ailments. We could correlate the reports that RAS plays a significant role in the prognosis of the disease.

Conclusions: Patients with cardiovascular diseases, diabetes mellitus and hypertension are at greater risk for developing COVID-19 infection. There may be massive derangement of the entire RAS after the attack of COVID-19 and hence, patients with these pre-existing comorbidities and on ACE inhibitors or angiotensin receptor blockers should be monitored carefully considering the role of RAS in the prognosis of COVID-19 infections.

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1. Introduction

With the first case of corona virus infection reported from Wuhan, China on 31 December 2019, there has been unprecedented outbreak of coronavirus disease (COVID-19). As on the last week of the April 2020, over 3 million cases of corona disease have been reported from 210 countries with 3–10% deaths [1]. Although, the first case was reported from China, COVID-19 became devastating in other countries with USA, Spain, Italy, Germany and France leading not only in the number of cases but also in number of deaths reported. The United Nations called COVID-19 pandemic the worst global humanitarian crisis since World War II. Countries all over the world are taking aggressive steps and adopting all possible preventive measures to prevent the spread of this disease. Half of the world population is under the lockdown in April 2020 as a measure to prevent the spread.

The first confirmed death was reported in Wuhan on 9th January 2020 [2]. The first death outside mainland China occurred on 1st February in the Philippines [3]. Soon it spread outside the Asia, in France on 14th February and by 13th March, more than forty countries and territories had reported deaths, in every continent except Antarctica [4,5]. The death numbers are so rampant that by the last week of April 2020, it has increased from 20,794 (in UK) to 54,881 (in USA). The death rate is again over 10% in as many as 20 countries around the world [6]. Even in India, as per the report of Ministry of Health & Family Welfare, Government of India, there were 7551 positive cases of COVID-19 as on 10 April 2020 (increased to over 30,000 in the last week of April 2020) 504 patients recovered and discharged and 206 deaths have occurred (Ministry of Health and Family Welfare, accessed on 10 April 2020, 08:00 GMT + 5:30).

Preliminary researches on COVID-19 illustrate that elderly or people with comorbidities like cardiovascular diseases, diabetes mellitus, cancer, hypertension, or lung diseases are at higher risk [7,8].The very first study conducted on 41 COVID-19 laboratory confirmed cases showed that 28 patients were discharged and six had died. Jordan et al. [9] described that around 25% of people including adults more than 70 years and those having existing health problems like respiratory disorders, cancer and cardiovascular diseases in United Kingdom are designated in high risk category. Chen et al. [10] conducted a study on a cohort of 799 Covid 19 affected patients admitted in the isolation ward of a hospital in Wuhan, China. The authors compared characteristics of 113 death cases with those of 161 recovered cases. The study concluded that the patients who died were around 17 years older than the patients who recovered. 83.7% of the deceased were males and had comorbidities like hypertension, cardiovascular diseases and diabetes mellitus etc.

One of the distinctive features with respect to deaths among COVID 19 patients was the association of COVID-19 with cardio-vascular diseases and diabetes reported from several parts of the world [11–13].The connecting link to this associated comorbidity has been the angiotensin-converting enzyme-2 (ACE2) receptor as its site of virus multiplication. Research for decades together has proved that ACE2 is expressed in epithelial cells of the lung, intestine, kidney and blood vessels [14]. The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, hypertension and it is the regulator not only of the blood pressure, inflammation and immune mechanisms but also a regulator of electrolyte balance. [15].

ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) are now the most commonly used drugs for hypertension, cardiovascular disorders and diabetes. Hence, worldwide this aspect has been considered and one of the strategies emerged was to consider the use of these drugs during the treatment and management of COVID-19 infection. Another strategy has been to develop antiviral newer drugs including the repurposing of the available drugs considering the ACE2 as the target. The question however remains is that in spite of all these attempts, the death rates are not getting decreased. Further, some of the clinical features appear to be similar throughout the world.

Common symptoms of novel coronavirus infection are fever, dry cough, nasal congestion, fatigue, diarrhoea, shortness of breath and breathing difficulty. In some cases, disease may lead to more serious respiratory conditions like bronchitis, pneumonia, respiratory failure or multiple organ failure. Chinese Centre of Disease Control and Prevention published a study conducted on 44,672 confirmed cases of COVID-19. It was concluded that 81% of the corona infected people had mild symptoms, 14% of the remaining were in severe conditions while 5% experienced critical illnesses like respiratory failure, septic shock or multiple organ failure. 2.3% deaths of the confirmed cases were reported. Also, only 2.2% of confirmed cases were less than 20 years old [16,17]. Previous researches on SARS and MERS described the association of age, gender and presence of comorbidities with mortality risk, with diabetes and cardiac diseases being the most imperative components to predict adverse outcomes [18]. Therefore, it is important to evaluate these parameters in COVID-19 also.

Finally, it is not clear whether the high number of deaths in patients with diabetes, and cardiovascular complications especially in old age males are because of the pre-existing comorbidities or because of overwhelming critical attack of COVID-19 on ACE2 resulted complications. Present paper is aimed to delineate the clinical characteristics and evaluate the prevalence of underlying comorbidities if any, in COVID-19 deceased patients in India and to get the clarity on to this question.

2. Materials and methods

We conducted a retrospective study with descriptive research design using different sources like the Covid 19 (www.covid19india.org) tracker that takes information from Ministry of Health and Family Welfare, Government of India, press releases of different states, official Government links, databases PubMed and Web of sciences until April 10, 2020. From 30 January (first COVID-19 case detected in India) to 10 April 2020, we explored details of first 206 death cases in India.

Out of 206 reported deaths, some data of 176 deceased could be obtained like their demographic, epidemiological, clinical and laboratory characteristics along with medical his-

tory, travel and exposure history and underlying chronic diseases. Out of 206 deaths reported as on 10 April 2020, these 176 death cases were analysed to delineate the clinical characteristics and evaluate the prevalence of underlying comorbidities if any.

3. Results

Results of the present study depict that as on 10th April 2020 number of deceased cases were highest in Maharashtra with Mumbai as its capital (98) followed by Gujarat with Ahmedabad as the metro city (17), Madhya Pradesh (16) and Delhi, the capital of India (13).

It was found that 5.1% of the deceased were less than 40 years old while 53.4% were more than 60 years old and 41.4% were between 40 and 60 years old. Age-wise deceased cases are shown in Fig. 1. Among the deceased, 69.3% (122) were males whereas 30.68% (54) were females i.e. death ratio of males to females was 2.25. This shows that male sex is more prone to coronavirus infection than females (Fig. 2).

It was found that 50.5% of the deceased patients had pre-existing comorbidities with diabetes to be present in 27.8% (49) of the deceased cases. The findings are consistent with those reported from other countries but the cases of diabetes are relatively higher. Among the deceased, 22.1% (39) were hypertensive which is another significant comorbidity. Also 13% had both diabetes as well as hypertension. It was interesting that only 13.6% (24) of the deceased were having pre-existing respiratory problems. 6.2% of the deceased had cardiac ailments. All three conditions i.e. diabetes mellitus, hypertension and cardiovascular disease were present in 2.8% of the deceased patients.

Clinical characteristics of 176 deceased patients are presented in Table 1. The percentage of comorbidities in Covid-19 deceased cases are depicted in Fig. 3. It was found that 9.7% (20) of the deceased patients were having travel history from the affected regions. The youngest causality of COVID-19 in India was fourteen months old boy from Gujarat's Jamnagar who died of multiple organ failure. A thirty years old pregnant woman is the first and only case to die of coronavirus infection during pregnancy in India. She was nine months pregnant and had pre-existing respiratory complications.

At the onset, fever and cough were the predominant symptoms in deceased patients. Some other prevalent symptoms included chest tightness, fatigue and dyspnoea while few less common symptoms were diarrhoea, myalgia and anorexia. Acute respiratory distress syndrome, respiratory failure, cardiac failure, sepsis and renal failure were some of the common complications that were observed in deceased.

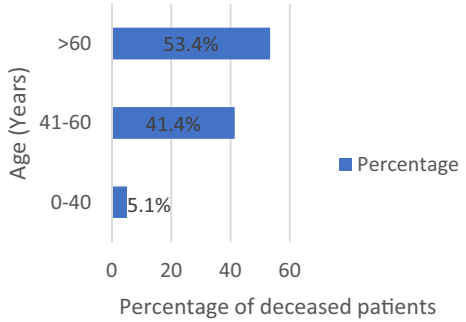

Fig.1 – Age-wise deceased cases of Covid-19.

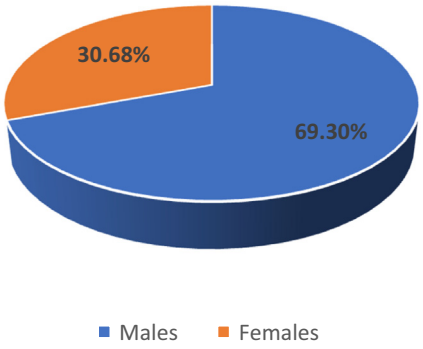

Fig.2 – Gender-wise deceased cases of Covid-19.

Table 1 – Characteristics of Covid-19 deceased patients in India as on 10April 2020 (176 cases with details).

Characteristics	Diseased cases (n = 176)
AGE	
<40 years	3.1%
41–60 years	41.4%
>60 years	53.4%
GENDER	
Male	69.3%
Female	30.68%
COMORBIDITIES	
Diabetes Mellitus	27.8%
Hypertension	22.1%
Respiratory ailments	13.6%
Both Diabetes & Hypertension	13%
Cardiac Illness	6.2%
Diabetes, Hypertension & Cardiac illness	2.8%
Kidney ailments	2.27%
Liver ailments	2.8%

4. Discussion and conclusions

The reports of 206 cases of deceased patients in India are consistent with those reported from other countries. The maximum number of patients were from the states with higher number of foreign travellers, densely populated cities like Maharashtra, Mumbai, Delhi, Gujarat and Uttar Pradesh. This indicated that crowding may play an important role in spreading COVID-19 infection. The above findings are consistent with the reports from other countries, similar to what reported in Paris in France, NewYork in USA.

As reported from most of the countries, around 53.4% of deaths included people aged above 60 years confirming that older people are at a higher risk of developing COVID-19 infection. One of the obvious reason for older people being more susceptible to COVID-19 may be the low immunity, weak pulmonary capacity and may be the ability to cope up with physiological changes that occur in the body with ageing. They are also more prone to have conditions like cardiac and lung

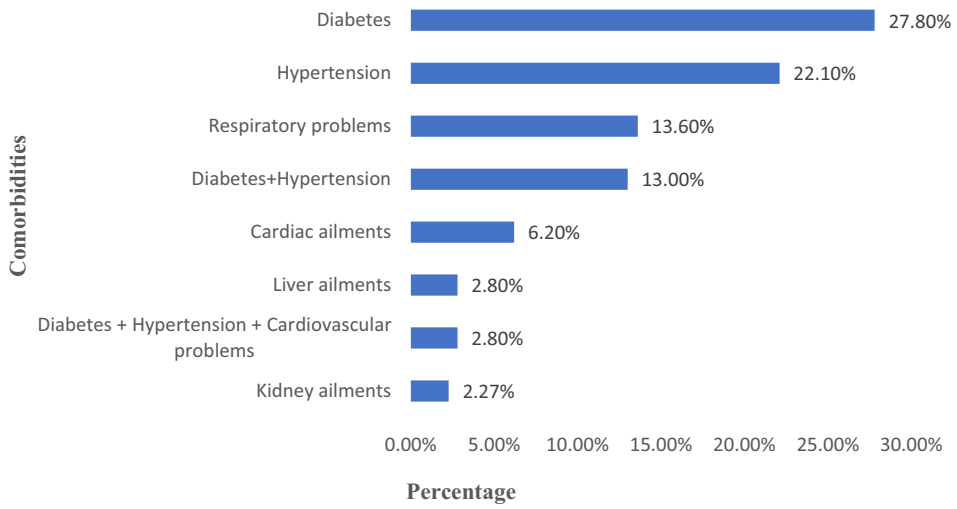

Fig. 3 – Percentage of Co-morbidities in Covid-19 deceased cases..

disease, diabetes mellitus or renal problems that weakens the ability of their body to fight with infectious disease.

Weak immune mechanisms coupled with cytokine surge is one of the major causes that finally leads to decreased cellular oxygenation at the level of alveoli, has been reported to be the main cause of death. Another pattern that is being observed in this research is gender differences i.e. males seem to hit harder and are more likely to have severe illness than females. This may be because of biological differences between men and women. Immune responses in women are more robust as compared to men due to the presence of estrogen hormone which is playing a protective role in immunity of the patients. Also since autoimmune diseases are more prevalent in women, they are more protected against new invading infections because of production of increased levels of antibodies that remain in the circulation for a longer time. Toll-like receptor (TLR)-7 is also higher in females leading to better immune responses and ultimately increased resistance to viral infections [19]. Another factor is that the presence of two X chromosomes in females emphasizes their immune system though only one X chromosome is active, while there is only one X chromosome in men [19,20]. A research on single-cell sequencing concluded that ACE2 (Angiotensin Converting Enzyme 2) gene expression was more predominant in males in Asia, which may be the reason that men are more susceptible to COVID-19 [21].

ACE2 is expressed by epithelial cells of the lung, intestine, kidney and blood [22]. Increase in expression of ACE2 has been reported in patients with type 1 or type 2 diabetes and hypertension and may be responsible for cardiomyopathy [23]. It is unclear whether the high rate of cardiomyopathy in this case series reflects a direct cardiac complication of SARS CoV-2 infection or resulted from overwhelming critical illness. Others have described cardiomyopathy in COVID-19, and further research may better characterize this risk [22,23]. In patients having type 1 or type 2 diabetes mellitus, if treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) have increased levels of ACE2 [14]. ACE inhibitors and ARBs are also used for the treatment of hypertension which results in an upregulation of ACE2 [15]. Thiazolidinediones and ibuprofen can also increase ACE2. This shows that ACE2 expression is increased in diabetes mellitus and treatment with ACE inhibitors and ARBs increases ACE2 expression facilitating COVID-19 infection [24]. It is also observed in our study that patients with cardiovascular diseases are more vulnerable for novel coronavirus infection. Previous studies also depict relationship between cardiovascular metabolic diseases and SARS and MERS infections [18,25]. ACE2 gene expression is also expressed in cardiovascular system and therefore, patients with existing cardiovascular diseases face a greater risk of COVID-19 infection and also affect the development and prognosis of pneumonia. Pneumonia leads to substantial gas exchange obstruction, causing hypoxaemia, which diminishes the energy supplied by cell metabolism and upsurges anaerobic fermentation. This causes destruction of phospholipid layer of cell membrane by intracellular acidosis and oxygen free radicals causing respiratory distress. Severe respiratory distress is considered to be the primary cause of COVID-19 induced death [26].

It is now identified that the SARS-CoV-2 utilizes Angiotensin Converting Enzyme(ACE)-2 receptors for endosomal formation and multiplication. This has attracted the attention of scientists to consider ACE2 as the target for the development of newer drugs for COVID -19 treatment. Many clinical studies and reports directly or indirectly prove this concept. The drug repurposing strategies have been utilized for getting effective medicine to treat the patients with COVID-19.

It is reported that despite the increase usage of 4-hydroxychoroquine, some non-specific anti-viral agents and even angiotensin receptor antagonists, corticosteroids, the mortality of the patients still remains unabated. In last one month over 105,771 patients have been reported to have died globally including 4958 deaths in G-7 countries [27]. In the absence of authenticated medicine available, clinical management of the patients in the ICU is a great challenge. There may be a desperate situation in these Critical care units. This calls for the out of box thinking. It is well established that

ACE2 is one of the important component of RAS that regulates cardiovascular system including renal vasculature, lungs, brain and retinal blood.

ACE 1 or the Angiotensin *per se* may not have direct role with COVID multiplication but its binding to ACE2 or the site is likely to cause disturbance in the regulation and function of RAS. Besides blood pressure control by angiotensin-1 or angiotensin-2, both are involved in immune mechanisms and cytokines control. Even the porphyrin and methhemoglobin like situation is likely to be produced with the disturbances in RAS.

It can be hypothesized that as a consequent to this there may be exaggerated increase in the expression of ACE2 that facilitates infection with COVID-19. It is now well accepted that COVID -19 binds to their target cells through ACE2. It needs to be emphasized that it is the receptor for ACE2 and not the ACE2 *per se*. ACE2 is expressed by epithelial cells of the lungs, kidneys, intestine and blood vessels. It is therefore, suggested that patients with cardiovascular diseases, diabetes mellitus and hypertension who are treated with ACE2 related drugs have the worst prognosis after COVID-19 infection. They should be monitored carefully for ACE2-modulating medications. Our research concludes that pre-existing comorbidities like diabetes, hypertension, respiratory and cardiac problems are strongly associated with poor outcome in COVID-19 affected patients. Patients having cardiovascular comorbidities are at higher risk of developing cardiac complications which highlights the significance of earlier cardiac monitoring and supportive care in such patients. Further, during the management of the patients in ICU, RAS should be considered not only from the point of new drug usage for the treatment of the patient but also the management of the serious patient of COVID-19 in ICU.

Several scientists and clinicians around the world are debating on the role of ACE2, however, it is necessary to consider **holistically the role of RAS when the ACE2 receptors are occupied by corona virus**. There is a controversy whether the ACE2 levels are increased or inhibited. There are no therapeutically proven inhibitors of ACE2. Angiotensin receptor blockers like losartan block vasoconstrictor and profibrotic though AT_1 receptors, but in turn they cause activation of AT2 receptors to produce vasodilatation. It is not clear whether because of COVID 19 there is inhibition of just receptors of ACE2 or ACE2 levels. It is well known that physiologically, there is short feedback control through renin on ACE2 production [28]. Further, ACE2 is also reported to be generated through an alternate pathway in heart and kidney [29]. The same possibility cannot be ruled out in abnormal circumstances in lung tissues. ACE2 is now known to regulate not only the vasculature but inflammation, oxidative stress, fibrosis and proliferation [29].

Cytokine surge leading to damage of alveoli and their functions of oxygen transport is one of the main causes of complications leading to multi-organ failure. Further, thrombotic events also appear to be high. These are known to occur in diabetics also and can be correlated with RAS. ACE2 is constitutively expressed by the epithelial cells of the lungs, kidney, intestine and blood vessels. ACE 2 is known to break down angiotensin-II and angiotensin-I into angiotensin (1–7) and angiotensin (1–9), respectively [30]. ACE2/Ang (1–7) system plays an important anti-inflammatory and anti-oxidant role protecting the lungs against infections [31]. However, it is possible that the increase ACE2 expression after COVID-19 may produce deleterious effects leading to severe lung injury and acute respiratory distress syndrome (ARDS) with COVID-19 [31].

The limitation of the paper is that small number of the deceased have been included with limited clinical details. Although comparison has been made to extend with other reports published, it is desirable that the hypothesis is tested with real time data.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Author contributions

Prof Ramesh K Goyal conceptualized and designed the study, Puneeta Ajmera and Jaseela Majeed drafted the manuscript and Prof Ramesh Goyal made final revisions, and all authors critically revised, read and approved the final manuscript.

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