SHORT COMMUNICATION

Do Mortality and Acute Respiratory Distress Syndrome due to COVID-19 are related to Pneumonia or Angioedema like illness?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) outbreak, arisen in Wuhan, China. It is very series disease.Started with pneumonia of unknown etiology whichhave been reported to the World Health Organization (WHO) on 31 December 2019. Novel coronavirus (2019-nCov) was identified and isolated by Chinese health authorities on 7 January 2020, and it was sharing the same receptor, Angiotensin-converting enzyme 2 (ACE2) as SARS-CoV,ACE2 RNA expression profile in the normal human lung and ACE2 virus receptor expression is concentrated in a small population of type II alveolar cells. This study highlights important questions regarding the pathophysiology, and treatment options of COVID-2019; firstly, is the dry cough associated with the course of illness of COVID-2019 due to the overproduction of bradykinin? Secondly, is the ARDS and mortality associated with COVID-2019 are due to pneumonia or angioedema like illness?
Keywords*:* COVID-2019;AT2-Receptor;Angioedema like illness**.**

INTRODUCTION

The diverse cases of pneumonia that have been detected in Wuhan City, Hubei Province of China are reported to the World Health Organization (WHO) on 31 December 2019. A novel coronavirus (2019-nCoV) was identified and isolated by Chinese health authorities on 7 January 2020, and it was sharing the same receptor, Angiotensin-converting enzyme 2 (ACE2), with SARS-CoV[1]. A recently study conducted by Zou, X. et a[2 succeed to establish a riskmap of human organs that invaded by the novel coronavirus, they analyzed the single-cell RNA sequencing (scRNA-seq) datasets derived from major human systems, such as respiratory, cardiovascular, digestive, and urinary systems. Through scRNA-seq data analyses, they identified the organs at risks, such as lung, heart, esophagus, kidney, bladder, and ileum, and located specific cell types (i.e., type II alveolar cells (AT2), myocardial cells, proximal tubule cells of the kidney, ileum, and esophagus epithelial cells, and bladder urothelial cells), which are susceptible to 2019-nCoV infection[2]. Based on the public database and the state of the art single-cell RNA-Seq technique, Zhao, Yu, et al[1], analyzed the ACE2 RNA expression profile in the normal human lungs. The result indicates that the ACE2 virus receptor expression is concentrated in a small population of type II alveolar cells (AT2). Surprisingly, they found that this population of ACE2-expressing AT2, also revealed high expression of other genes that are positively regulating viral reproduction and transmission. Zhao et al[1] demonstrated that one of eight Asian individuals showed an extremely large number of ACE2-expressing cells in the lung. In one study by Imai Kuba et al[3] reported that (ACE2), and the angiotensin II type 2 receptor (AT2 R) protects mice from severe acute lung injury induced by acid aspiration or sepsis. However, other components of the renin-angiotensin system, including ACE, angiotensin II, and the angiotensin II type 1a receptor (AT1a), promote disease pathogenesis, induce lung edemas and impair lung function. Interestingly, when the AT1 receptor is blocked, local free AT2 levels will rise particularly around the AT2 receptors and this termed yin–yang effect[4]. The AT2-receptor seems to have a role in apoptosis, embryonic development, and neuronal regeneration of tissues after injury, in angiogenesis, cellular differentiation, growth inhibition, and possibly vasodilatation[5]. The anti-inflammatory effects of AT2-receptor activation are associated with its signaling pathways involving the formation of nitric oxide and activation of phosphatases, and these effects promote cell survival and tissue function[6]. Studies during the SARS outbreak have demonstrated that ACE2 can protect murine lungs from acute lung injury as well as SARS-Spike protein-mediated lung injury, suggesting a dual role of ACE2 in SARS infections and protection from Acute Respiratory Distress Syndrome ARDS[7]. A case-control study among ARDS found that the renin angiotensin system(RAS) inhibitor group showed better survival rates than the non-RAS group ($P < 0.001$), and this study concluding that angiotensin converting enzyme (ACE) inhibitor or angiotensin enzyme blockers (ARB) may have a beneficial effect on ARDS patients[8].

Angioedema: The crucial adverse drug reaction of angiotensin-converting enzyme inhibitors (ACEIs) is angioedema and this occur due to decrease in bradykinin degradation. The angiotensin-converting enzyme is responsible for conversion of angiotensin I to angiotensin II. It is additionally responsible for the degradation of bradykinin, which is generated from high molecular weight kininogen by kallikrein[9]. By means of bradykinin 2 receptors, bradykinin cause vascular permeability and stimulates the release of substance P, a peptide that causes vasodilation and fluid extravasation into tissues. Inhibition of the angiotensin-converting enzyme and further blockade of bradykinin degradation is probably explained ACEI-induced angioedema[10]. Regardingcoagulopathies some studies revealed many patients with severe COVID-

19 attend with coagulopathies that associated with an increased risk of death[11]. A defective procoagulant and anticoagulant balance predisposes to the development of microthrombosis, disseminated intravascular coagulation (DIC), and multiorgan failure. In severe COVID-19 pneumonia with raised D-dimer level being a poor prognostic feature and DIC common in non-survivors[12].

Incidence and Mortality rate in blacks: Previous studies report that angioedema risk was significantly highest among blacks, more likely those older than 65 years. Although it is most likely to occur early after initiation of therapy, it may occur at any time, also among smokers, women, and those with a history of drug rash, seasonal allergies, and use of immunosuppressive therapy[13-15]. The Johns Hopkins University and American Community Survey indicate that to date, the mortality rate is higher 6-fold inblack counties than in white counties. Although they stated that it is primary data, it will give hint to the general situation[16]. Another review study in the state of Connecticut indicates that Blacks have a higher rate of infection and death in comparison to their population percentage[17]. International and UK data suggest that Black, Asian and Minority Ethnic (BAME) groups are at increased risk of infection and death from COVID-19[18].

CONCLUSION

Interfering of 2019-nCov with Renin-Angiotensin System (RAS) raising questions regarding the pathophysiology, and treatment options of COVID-2019, firstly, is the dry cough associated with the course of illness of COVID-2019, is it due to overproduction of bradykinin? Secondly, is the ARDS and mortality associated with COVID-2019 are due to pneumonia or angioedema like illness? Taking into account the different vulnerable organs invaded by the virus especially the heart.

Recommendation: Plasma exchange could be helpful as a treatment of thrombotic microangiopathy by delivering high volumes of plasma, replenishing missing factors (eg, ADAMTS-13 or complement proteins) and removing excess inflammatory mediators; however, this treatment needs to be further evaluated in a controlled trial setting[11]. Therapeutic options for angioedema due to C1-inhibitor deficiencies are C1-inhibitor concentrates, icatibant, and ecallantide. If these drugs are not available, fresh frozen plasma can be considered. All these medications have been used also in ACE inhibitor-induced angioedema with variable results thus they are not currently recommended whereas experts agree on the discontinuation of the causative drug[19].

Till evidence be available, shift all patients taking ACEIs for any cardiac morbidity into ARBs. C2 & C4 complement protein should be measured for every admission of COVID-2019 to decrease level of those proteins is a good surrogate to evaluate patients for angioedema. A retrospective cohort study can be conducted to pick up the effect of ARBs on the survival rate among 2019-nCoV who using those drugs for other conditions before the course of illness.

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