COVID-19 Epigenetics and Implications for Public Health

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**Abstract:** Background: COVID-19 debilitated communities globally in varying complexities and capacities in recent months.

**Objective:** The epigenetic changes in the COVID-19 patients were discussed in this article to explore various processes contributing to disease severity and elevation of risk due to infection.

**Methods:** Percentages of hospitalization, with and without intensive care, in the presence of diseases with increased ACE2 expression, were compared on the best available data. Further analysis compared two different age groups, 19-64 and ≥65 years of age.

**Result & Conclusion:** The COVID-19 disease is observed to be the most severe in the 65 and-higher-age group with pre-existing chronic conditions. This observational study is a nonexperimental empirical investigation of the outcomes of COVID-19 in different patient groups. Results are promising for conducting clinical trials with intervention groups. To ultimately succeed in disease prevention, researchers and clinicians must integrate epigenetic mechanisms to generate valid prescriptions for global well-being.

**Keywords:** COVID-19, epigenetic, communicable and non-communicable disease, chronic illness, public health, SARS-CoV-2.

**1. INTRODUCTION**

Chronic illnesses and infectious diseases have long impacted global health or economic well-being. This article discusses epigenetic and the future of what “communicable” and “non-communicable” diseases may have in common about human health. Preventing chronic disease, improving the human body’s responses to exposures including contact with infectious agents, and delaying disease burdens are the principle set of motives to invest in public health research, practice, and reformed policy. The ability to test for variation holds the potential for explaining the differences in responding to infectious diseases. Next-generation sequencing (NGS) may be an effective technology for combatting viruses, bacteria, fungi, parasites, animal vectors, and human hosts [1, 2]. The research suggested that NGS has been used to identify pathogens, providing insights into virulence, the transmission of infectious diseases, and antimicrobial resistance [3, 4]. The current article is an effort to discuss epigenetic changes in the host in response to the novel coronavirus (nCOVID-19). This pandemic-causing infectious agent globally incapacitated communities in varying complexities and capacities.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously referred to as the 2019 novel coronavirus (2019-nCoV), linked with pneumonia, was first reported in Wuhan of the Hubei Province in China on December 12 of 2019 [5]. The virus continues to pose a severe threat to public health worldwide. United States Centers for Disease Control and Prevention (CDC) assesses risk factors for severe COVID-19 illness and notes that being 65 years-of-age and older or having serious underlying medical conditions may worsen the course. Living in long-term care facilities, being of any age but with medical conditions such as obesity, diabetes, chronic lung disease, asthma, heart conditions, chronic kidney disease, liver disease, dialysis, immunocompromised cancer, smoking, transplantation, immune deficiencies, human Immunodeficiency Virus /Acquired Immunodeficiency Syndrome (HIV/AIDS), prolonged use of corticosteroids and medications have been associated with poor outcomes. Moreover, smoking has been reported to contribute to disease severity and elevate the risk of death from COVID-19. Patients 65 or older, especially individuals over 85, appear to be at higher risk. Females appear to be less susceptible to viral infections based on sex hormones and the X chromosome, which play essential roles in innate and adaptive immunity [5-12]. One of the most critical factors in determining the severity of the COVID-19 infection is the cell entry pathway. Angiotensin-converting enzyme 2 (ACE2) is shown to be the host cell entry receptor for COVID-19 at the onset of the disease. This receptor also is located in a variety
of human tissues, including the lung, liver, stomach, ileum, colon, and kidney [13].

The high-risk group for COVID-19 severity consists of obese individuals and those with diabetes mellitus (DM), cardiovascular disease (CVD), neurodegenerative disorders, cancer, immunocompromised conditions, which are also linked to epigenetic modifications from environmental factors [11-14].

There is evidence of epigenetic changes in ACE2 protein expression in virtually all of these conditions, and quite notably, ACE2 is shown to be the entry receptor for COVID-19 in the human body. Researchers reported in March 2020 that ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19 [15].

Investigators of the current analysis propose the corollary that epigenetic processes contribute to disease severity and elevate the risk of death from COVID-19. This research aims to refer to epigenetic processes to shed light on mechanisms involved and to elaborate on differences in individual immunity responses in the COVID-19 infection. Proposing a possible link, the correlation between COVID-19 and epigenetic mechanisms has been investigated in search of valid evidence.

2. MATERIALS AND METHODS

In the current study, the distribution of risk factors reported for the severe course for COVID-19, in relationship with diseases associated with epigenetic changes, was assessed. Early reports on COVID-19 provide information on underlying medical conditions that are linked to the more severe end of the disease spectrum. COVID-19 patients in need of intensive care or other inpatient hospital services were evaluated concerning diseases where ACE2 expression is increased [10, 15].

3. RESULTS

Chronic diseases accompanying severe respiratory infection from COVID-19 were 10.9% for diabetes, 9.2% for chronic lung disease, and 9.0% for CVD in the US (Table 1). The percentage of hospitalization and Intensive Care Unit (ICU) admissions for COVID-19 patients with underlying chronic disease is observed to be higher than COVID-19 patients without the chronic disease (Table 1, Table 2).

The percentages of hospitalization and ICU admissions from COVID-19 infection were evaluated for two different age groups and patients with or without preexisting chronic conditions. The rate of hospitalization is 41.7-44.5% for those who are 65 years of age and older with underlying health conditions when compared to 16.8-18.3% for COVID-19 patients in the same age group but without underlying health conditions. For ages 19-64, hospitalization without ICU is 18.1-19.9% for COVID-19 patients with underlying health conditions, who are at higher risk when compared to 6.2-6.7% in the same age group but without an underlying health condition. People who are 65 years old and older are at higher risk for severe illness from COVID-19. The risk is even higher in the presence of underlying health conditions (Table 2). During COVID-19 infection, the lung shows the acute respiratory distress syndrome (ARDS) re-

<table>
<thead>
<tr>
<th>Disease with Increased ACE2 Expression</th>
<th>Underlying Health Condition / Risk Factor for Severe Outcomes from Respiratory Infection (%)</th>
<th>Non-ICU* Hospitalization for COVID-19 with Underlying Medical Conditions (%)</th>
<th>ICU* Admission for COVID-19 with Underlying Medical Conditions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>10.9</td>
<td>38.0</td>
<td>18.0</td>
</tr>
<tr>
<td>CVD</td>
<td>9.0</td>
<td>37.0</td>
<td>20.0</td>
</tr>
<tr>
<td>65+ with an underlying health condition</td>
<td>32.0</td>
<td>44.5</td>
<td>22.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.3</td>
<td>27.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>9.2</td>
<td>23.0</td>
<td>24.0</td>
</tr>
</tbody>
</table>
*Intensive Care Unit (ICU)

<table>
<thead>
<tr>
<th>Ages</th>
<th>Hospitalization without ICU*</th>
<th>Hospitalization with ICU*</th>
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<tbody>
<tr>
<td></td>
<td>with UHC</td>
<td>without UHC</td>
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<tr>
<td>19-64</td>
<td>18.1-19.9</td>
<td>6.2-6.7</td>
</tr>
<tr>
<td>≥65</td>
<td>41.7-44.5</td>
<td>16.8-18.3</td>
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</tbody>
</table>
*Intensive Care Unit (ICU)
lated to age. Most patients require endotracheal intubation and positive pressure ventilation. Previously, the development of ARDS is generally associated with several clinical disorders, including sepsis, pneumonia, aspiration of gastric contents, and significant trauma [16, 17].

The ARDS were best described in a classic study in 1977 that included ultrastructural details at different time points in the acute, subacute, and chronic phases (Fig. 1) at the characteristic pathological findings in the lungs of patients [3, 18].

In the acute phase (the first 1-6 days), the syndrome triggers the accumulation of neutrophils, macrophages, and red blood cells in the alveoli, which is the evidence of interstitial and alveolar edema.

The undressing of the alveolar epithelium is the evidence of both endothelial and epithelial injury. There are prominent hyaline membranes in the alveoli as well. In the subacute phase (the next 7-14 days), after limited reabsorption of the edema, the proliferation of alveolar epithelial type II cells shows that the cells make an attempt to repair. There may also be infiltration of fibroblasts and some evidence of collagen deposition. In the chronic phase (after 14 days), there is a resolution of the acute neutrophilic infiltrate (unless there has been superimposed nosocomial pneumonia) with more mononuclear cells and alveolar macrophages in the alveoli, and often increased fibrosis with evidence of alveolar epithelial repair (Fig. 1). In many patients, resolution progresses without fibrosis and directly with gradual resolution of the edema and acute inflammation.

4. DISCUSSION

COVID-19 disease is found to be the most severe in the age group of 65 years and a higher-age group with preexisting chronic conditions. Chronic illness raises clinical risk from COVID-19. This is a preliminary study, an analysis based on an initial report on the virus. Researchers of the current study observed the effects of epigenetic risk factors on disease severity. Epigenetic modification is known to be reversible modifications in most cases. The influence of harmful exposures on human epigenetic regulation may turn out to be a rewarding field of study for future research, as the underlying mechanism draws clinicians and researchers to the age-old question, “Which came first: the chicken or the egg?”. The spread of COVID-19 once again provides evidence that environmental exposure has a role in coping with diseases in later life. Environmental Epigenomics and disease susceptibility continue to raise concerns about a plausible link between the environment and alterations in gene expression that might lead to disease severity in senior life [19].

This observational study is a non-experimental empirical investigation of the outcomes of COVID-19 in different patient groups. Results are promising for conducting clinical trials with intervention groups.

An essential limitation of the study was that reliable data is yet unavailable for COVID-19, the novel coronavirus, as countries continue to cope with the burdens of disease from this new virus strain. The virus was unknown to humankind before the first report from China in December 2019. Results from initial reports are carefully monitored around the world.

The host COVID-19 receptor is ACE2, which regulates with epigenetic changes, is located on the X chromosome [20, 21]. Studies suggest that epigenetic changes of ACE2 are controlled by DNA methylation. ACE2's DNA methylation levels are associated with gender and tissue types. ACE2 gene studies showed that females were especially hypomethylated compared to males, hence the declaration that

![Fig. (1). The healthy alveolus (left side) and the injured alveolus (right side) in the acute phase of acute lung injury and acute respiratory distress syndrome (This figure is adapted from Ref. [18]). (A higher resolution / colour version of this figure is available in the electronic copy of the article).](image-url)
COVID-19 has different gender-related outcomes, in favor of women. These gender-related baseline differences in the DNA methylation associated with the ACE2 gene in lung tissues require further investigation, particularly in the context of the ACE2 gene and protein expression and COVID-19 severity [13].

Some studies indicate that COVID-19 virus-related disease severity and mortality increase with age, and this may be due to epigenetic changes in the immune system in older generations. There is mention of an “epigenetic clock” and DNA methylation-related illnesses in older age groups. Another study shows a possible relation between COVID-19 disease severity and epigenetic age acceleration, which is a known mechanism for viral infections. Changes in DNA methylation levels at CpG sites, which are located in subtelomeric loci and control innate immunity, are responsible for aging as an epigenetic phenomenon. Epigenetic changes possibly mediate inflammatory responses to COVID-19 [22-24]. Epigenetic changes in the immune system may adequately explain COVID-19 disease severity.

A separate study provided evidence in lupus patients to suggest that hypomethylation and ACE2 overexpression, i.e., epigenetic dysregulation of interferon-regulated genes, might increase COVID-19 susceptibility and severity in this patient group. ACE2, which encodes a functional receptor for the SARS-CoV-2 spike glycoprotein, is located on the X chromosome. Oxidative stress induced by viral infections exacerbates the DNA methylation defect in lupus, possibly resulting in further ACE2 hypomethylation and enhanced viremia. Besides, the demethylation of interferon-regulated genes, NFκB, and essential cytokine genes in lupus patients might exacerbate the immune response to SARS-CoV-2 and increase the likelihood of the human body's overreaction, called the “cytokine storm”. Immunologic mechanisms in the pathogenesis may be interrelated [24, 25].

Older age, diabetes, severe obesity, and chronic lung disease increase morbidity and mortality in COVID-19 patients. Causal association with lung ACE2 expression enhancement and susceptibility to COVID-19 have been shown, but the significance of ACE2 expression on COVID-19 pathogenesis and mortality is yet not be fully explained. The importance of ACE2 expression on COVID-19 pathogenesis and mortality is not known [25-28].

There are many similarities between SARS-CoV and MERS-CoV infections. Acute respiratory distress syndrome (ARDS), which is a type of respiratory failure, is characterized by rapid onset of widespread inflammation in the lungs, multiple organ failure, resulting in the release of large amounts of proinflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL6, etc.) and chemokine in severe SARS-CoV-2 infection and an intense and uncontrolled systemic inflammatory response that can cause death in response to both infectious agents. In a case series with COVID-19, the cause of death in six out of 41 cases (14.6%) was reported to be ARDS [4, 29]. A further aspect that should be investigated is the genetic predisposition for an increased risk of SARS-CoV-2 infection, which might be due to ACE2 polymorphisms that have been linked to DM, cerebral stroke, and hypertension, especially in Asian populations. Summarizing this information, the sensitivity of an individual might result from a combination of both therapy and ACE2 polymorphism [30-32].

Recently, patients with Kawasaki-like disease have been reported to test positive for COVID-19. From an epigenetic perspective, toll-like receptor (TLR) genes encoding TLR1, TLR2, TLR4, TLR6, TLR8, and TLR9 were found to be hypomethylated in Kawasaki disease (KD) patients compared with healthy febrile controls. Based on information accumulated so far, researchers of this article approach COVID-19 mechanism of action to impact the immune system and show its after-effects on the host immune system, possibly driving the individual prone to secondary autoimmune diseases [33-35].

Many DNA viruses, along with some RNA viruses, have been shown to antagonize the regulatory machinery of the host epigenome. This mechanism creates regulated changes in the host's gene expression, which may adversely constitute favorable environments for virus spread and replication [36]. COVID-19 follows a more severe course in people with epigenetic changes, due to autoimmune diseases such as KD, secondary to the infection.

The outcome of the study points towards a plausible relationship between the COVID-19 and epigenetic factors are still the missing link and further analysis will affirm the possible correlation with logical explanations, aiming to improve the human body's responses to infections. Nevertheless, this article reiterates the proposition that the epigenetic resolution of host-virus interactions is worth the researchers' attention to present solutions for a variety of diseases. Epigenetics, genomics, and precision health may evolve into disciplines to achieve the global public health agenda [37, 38].

CONCLUSION

Methylation of ACE2 in COVID-19 patient- may be associated with “super spreaders” and enhanced transmissivity. This information will be vital for vaccine development and epigenetic therapeutics against COVID-19. Raising awareness about environmental conditions that cause DNA methylation and other epigenetic changes of children and adolescents will increase social protection against viral outbreaks that may occur in older age, diabetes, obesity, and CVD. Lungs may present as ground zero for COVID-19 entrance; however, the article questions whether the immune system of each individual is under attack in varying capacities? The answer may be hidden in the genome itself. Infectious and chronic diseases are public health threats that impact masses in a globalized world. To ultimately succeed in disease prevention, researchers and clinicians must integrate epigenetic mechanisms to generate a valid prescription for improving global welfare.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.
CONSENT FOR PUBLICATION
Not applicable.

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REFERENCES


