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Review article

COVID-19: Why does disease severity vary among individuals?

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ABSTRACT

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is responsible for the current pandemic, coronavirus disease 2019 (COVID-19). While all people are susceptible to the SARS-CoV-2 infection, the nature and severity of the disease vary significantly among individuals and populations. Importantly, reported disease burdens and case fatality rates differ considerably from country to country. There are, however, still uncertainties about the severity of the disease among individuals or the reason behind a more severe disease in some cases. There is a strong possibility that the severity of this disease depends on a complicated interaction between the host, virus, and environment, which leads to different clinical outcomes. The objective of this article is to point out the essential influential factors related to the host, virus, and environment affecting the clinical outcome of COVID-19.

1. Introduction

Today, the world is fighting against a devastating pandemic caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus causes a complicated respiratory disease, now called coronavirus disease 2019 (COVID-19). As of today, (Jan 25, 2021), there are 99.1 million of confirmed cases and over 2.13 million reported deaths due to COVID-19, worldwide. The majority of infected cases present asymptomatic or mild symptoms, while the minority of cases shows severe or critical outcome and some, unfortunately, die [1,2]. Although older patients with underlying diseases seem to be more susceptible to severe illness and death [3], several cases of life-threatening infection occur among healthy individuals with no health-related concerns [4]. Therefore, there are some crucial yet unanswered questions such as, why does disease severity vary among individuals? and why do some individuals get a more severe disease? Indeed, there is a missing, probably multiple, behind this discrepancy.

There are many factors related to the host, virus, and environment that may address the complexity of COVID-19 clinical phenotype [5,6]. The exact influence of host factors, specifically, genetic makeup, has remained mostly unknown. There is, on the other hand, a little data available about the pathogenesis of SARS-CoV-2 and there are only some initial assumptions about the virus behavior [2]. The significant role of environmental factors is also in its infancy. We are just beginning to uncover how host, viral, and environmental factors interact with each other and affect the infection. In this article, we discuss essential factors affecting the susceptibility and disease severity of SARS-CoV-2 infection. Understanding the underlying mechanisms behind the complicated disease phenotype is of the highest importance today and will be essential in identifying high-risk groups. Although there is little data available about SARS-CoV-2, our experience and knowledge from similar viruses can bring insightful information to the scientific community.

2. Host factors

Since a strong protective immune response is essential to eliminate the virus before its progression to more severe stages, the host's good general health state is undoubtedly critical. As such, people of any age, especially older adults with comorbidities such as chronic bronchitis [7], diabetes [8], hypertension [9], cardiovascular disease [10], lung and liver diseases [11], chronic kidney disease [12], and chronic obstructive pulmonary disease (COPD) [13] may experience a more severe disease. Moreover, conditions and treatments that compromise

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the immune system, such as cancer treatment, bone marrow or organ transplantation, and prolonged use of corticosteroids, may also contribute to a higher risk of the disease, more severe outcomes, and even death [14]. Although epidemiological findings in some studies did not provide any evidence to more spread of SARS-CoV-2 among patients with asthma [14,15], it seems that patients with non-allergic asthma suffer from a more severe COVID-19 than patients with allergic asthma [16]. Importantly, metabolic syndrome is a cluster of conditions including abdominal obesity, elevated blood pressure, dysglycemia, atherogenic dyslipidemia, pro-thrombotic state, and proinflammatory state, which could affect the outcome of any disease. In this case, the worsened outcome of the disease may be due to the three components of this syndrome: hypertension, type 2 diabetes mellitus, and obesity that are mentioned as risk factors in the severity of COVID-19 [17]. Beside these well-known risk factors, there are other host-related conditions that may affect the outcome of COVID-19.

2.1. Lifestyle

It is believed that people's lifestyles significantly influence the disease course and its outcome [18,19]. Harmful health behaviors such as sedentary behavior with reduced physical activity, overeating, elevated alcohol and tobacco consumption, and increased screen time causing impaired sleep are associated with non-communicable diseases and can interfere with immunity system behavior [20]. It is reported that the higher physical fitness, better health, lower inflammation, better redox balance, and longer leukocyte telomere length in master athletes can help them to face COVID-19 with a stronger health state comparing to their frail sedentary age-matched peers [21]. Severe obesity puts people at a higher risk for complications from COVID-19 by increasing the risk of acute respiratory distress syndrome (ARDS) [22]. Moreover, obesity makes people prone to multiple chronic diseases and underlying health conditions that can potentially increase the risk of severe disease [23]. It is essential to have regular and moderate exercise during the pandemic to prevent the health risks associated with physical inactivity, increase wellbeing and immunity, and reduce stress and anxiety [18,24].

2.2. Smoking

To date, smoking has been associated with several respiratory diseases and poor prognosis [25]. Tobacco smoking increases the susceptibility to infections by altering the host's mechanical and immunological defense [26]. Structural changes in the respiratory tract, including increased mucosal permeability and disruption of the respiratory epithelium, almost contribute to the development of respiratory tract infections and further complications [27]. For the COVID-19, many studies suggested an association between smoking with negative progression and adverse outcomes of the disease [28–30]. Smokers, especially former smokers, have a significantly higher angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) expression [31,32]. On the contrary, data from recent studies suggest that active smokers are underrepresented among patients with COVID-19 [33,34]. The protective role of smoking in COVID-19 is suggested due to some plausible mechanisms such as an anti-inflammatory effect of nicotine, a blunted immune response in smokers (reducing the risk of a cytokine storm in COVID-19), and increased nitric oxide in the respiratory tract (which may inhibit replication of SARS-CoV-2 and its entry into cells) [35]. However, it is suggested that the reported data are questionable with several biases and knowledge gaps, which necessitate further investigations on this matter [35].

2.3. Gender

The risk of a severe disease seems to be higher in male patients than in female patients, possibly because of genetic, hormonal, and immunological differences between the two genders [31,36,37]. In a recent study, men had more than 50% risk of getting severe COVID-19 infection and ICU admission than women [38]. The impact of sex steroid hormones on the T-helper 1/T-helper 2 cytokine balance is associated with the severity of most infectious diseases in males [39]. Also, males are at a higher risk of diseases caused by deleterious X-linked alleles. Interestingly, the expression level of ACE2, as an X chromosome encoded gene product, is found to be more in males than females [40,41]. Although the role of this relation in the disease severity has not yet been explicitly proven in COVID-19 patients, the higher expression of the ACE2 in males may be attributable to the elevated mortality rate in this group [42,43]. However, pregnant women are more sensitive to infections, especially viral infections, due to many biological and mechanical alterations during pregnancy [44]. As the T-helper 2 system is much more dominant in pregnant women for the fetus's protection, it makes the mother more susceptible to viruses because of the critical role of the T-helper 1 response in viral infections [45].

2.4. Age

All people of any age are affected by the SARS-CoV-2 infection. Beside All above-mentioned risk factors, the over-activation of NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome, by increasing hyperinflammatory cascade, in aged individuals seems to play an essential role in the higher lethality in this group [46]. Preliminary evidence suggests that children suffer from less severe COVID-19, which could be because of their lower intensity of viral exposure and lower expression of ACE2 and TMPRSS2 receptors in their upper and lower airways [32,47]. A still-developing immune system with relatively lower levels of inflammation-driving cytokines, absence of high-risk factors, and more pulmonary stem cells that are capable of repairing the damaged cells, could be other possible reasons for this observation [2,48]. Besides, COVID-19 might be milder in children due to the cross-immunity generated from seasonal coronaviruses [49], and their exposure to different vaccines throughout their lives [50].

2.5. Vaccination

There is substantial epidemiological evidence indicating that people's vaccination background could influence the COVID-19 outcome [51]. In this context, the Bacillus Calmette-Guérin (BCG) vaccine may significantly diminish the severity of the COVID-19 or even prevent the disease [52]. It is demonstrated that in countries and regions with national BCG vaccination programs, the number of involved people, and the pattern of death due to COVID 19 were relatively low [53]. Two mechanisms have been considered to explain this non-specific effect: trained immunity and heterologous immunity [52]. The "trained immunity" of such vaccines refers to the vaccine-induced histone modifications and epigenetic reprogramming at the promoter sites of genes encoding inflammatory cytokines and invigorating innate antimicrobial mechanisms [54]. The process results in an inhibited viral replication and a decrease in viral load and symptoms [53,55]. In heterologous immunity, cross-reactivity of the host immune response elicited by the vaccine antigens improved response against non-mycobacterial pathogens. However, further protection by BCG vaccination against viruses has been demonstrated in studies using animal models and it cannot be necessarily concluded that such effects can be observed in human [52]. Moreover, some studies provide some evidence suggesting that ecological studies about less COVID-19 in countries with routine BCG immunization are based on population rather than individual data, so that it can be confounding [56]. As another live attenuated vaccine, the Measles-Mumps-Rubella (MMR) can help prevent worsen outcomes of COVID-19 because of its capability to induce "trained" non-specific innate immune cells like the BCG vaccine [57]. The common features between MMR viruses and SARS-CoV-2 such as transmission and their primary replication in the upper respiratory tract and cross-protective

innate immunity offered by MMR vaccines, led to reconsidering MMR vaccination for immuno-prophylaxis against COVID-19 [58]. The ability of past vaccinations to generate immunity against non-self antigens provides a preferred condition for the immune system to increase the specific immunity against SARS-CoV-2 infection [35].

2.6. Genetics

Many of the severe COVID-19 cases do not demonstrate any of the above-mentioned host-related risk factors [59,60]. A recent modeling study indicates that 50% of the variance of the 'predicted COVID-19' phenotype is due to genetic factors [61]. Differences in genetic makeup can affect each individual's response to infection, leading to the wide variance in the infection outcome. As an example, the variable expression pattern and genetic variations of ACE2 receptor among different individuals might be associated with the severity of COVID-19 [40,62]. The ACE2, as a functional receptor for SARS-CoV-2, has a dual role during SARS-CoV-2 pathogenesis; its increased expression level can be a risk factor for the development of COVID-19 infection, and its reduced expression during COVID-19 leads to ARDS [63]. There is a decline of ACE2 expression from Europeans to Asians, suggesting a relationship between the decreased numbers of this genotype and the higher number of deceased cases in European countries such as Italy [64,65]. Also, ACE I/D allele frequency is entirely different in the ratio worldwide among different regions. Interestingly, a study reported a correlation between the increased I/D allele frequency and the recovery rate [65]. However, the frequency of the D allele in Africa, Europe, America, and Arab regions is more than in East Asia. Thus, a high frequency of the D allele may be related to the disease severity [65].

Interestingly, recent data from China declared that individuals with blood group A are at a higher risk of getting COVID-19, compared to those with blood type O [66]. However, there were some limitations to this study; the selected population for the investigation was fairly small, pre-existing medical conditions that can be effective on the severity of COVID-19 was not considered, and the control population groups lacked information such as age and sex [66]. It is also demonstrated that individuals with O blood group seem to have lower levels of ACE and higher ACE2 activity, which makes them less likely to develop severe COVID-19 [67]. Furthermore, in a study, rare putative loss-of-function variants of X-chromosomal Toll-like receptor 7 (TLR7) possibly associated with impaired type I and II interferon (IFN) responses were reported in young male patients with severe COVID-19 [68]. Besides, a cohort study on young COVID-19 patients suggested that a defective A91V perforin variant could be responsible for severe outcomes of the disease. In this case, as the variant may have an association with the decreased effectiveness of CD8 and NK cells, the ineffective SARS-CoV-2 clearance favoring the progress to a severe COVID-19 [69]. Finding a relationship between host differences and the clinical consequence of SARS-CoV-2 infection may be necessary to identify high-risk individuals.

3. Viral factors

SARS-CoV-2, as a coronavirus, has a single strand, positive-sense RNA genome with 29.8–29.9 kilo-bases length [70]. Generally, the virus is replicating similar to other coronaviruses and mutating at a rate as expected for other RNA viruses; the estimated average evolutionary rate for SARS-CoV-2 is 1.20×10^{-3} nucleotide substitutions per site per year, with mutations arising during every replication cycle [71]. The result of virus replication is the production of different mutants, and natural selection is decisive about which one will be predominant. Notably, a study has recently claimed that there are two types (S and L) of the virus, where L type is suggested to be more aggressive and spread more quickly [72]. Another study also mentioned three central variants named A, B, and C, of which A is the ancestral type according to the bat outgroup coronavirus [73]. However, there is a little data on whether the severity of COVID-19 is dependent on viral determinants such as genetic variation, viral load, and coinfection.

3.1. Genetic variation

The reported sequences from different countries showed high homology, with greater than 99% nucleotide and amino acid sequence identity [74]. To date, many mutations reported; however, none of them are associated with a significant change in virus behavior or virulence, and the information continues to emerge [72,75,76]. It has been reported that the D614G mutation increased in frequency and distribution worldwide and became the globally dominant form of SARS-CoV-2 [77]. The G614 mutant is found to be associated with higher levels of viral nucleic acid in the upper respiratory tract in human patients, suggesting higher viral loads and higher infectivity [72,77]. Later, another variant, which was possibly transmitted to humans from farmed minks, was identified in Denmark, provoking concerns about reducing virus neutralization in humans. However, the studies are ongoing, and to date, following many investigations and surveillance, this new variant does not appear to spread widely [76,78]. Surprisingly, emersion of a new variant in the United Kingdom called SARS-CoV-2 VOC 202012/01, as the variant of concern, was reported on December 2020. This variant contains 23 nucleotide substitutions and is not phylogenetically related to the common circulating SARS-CoV-2 virus in the United Kingdom when the variant was detected. Further investigations suggested that SARS-CoV-2 VOC 202012/01 has increased transmissibility with no disease severity change [76,79]. Moreover, 501Y·V2 is a new variant that is detected most recently in South Africa. In this case, genomic data highlighted that this variant rapidly displaced other lineages in South Africa. Also, preliminary studies suggested that the 501Y·V2 variant is associated with a higher viral load and, consequently, maybe with higher transmissibility. However, there is no clear evidence of any changes in the disease severity at this stage due to this new variant [76,80]. The potential risk of changing the virus virulence during the pandemic is vital and needs further investigation.

3.2. Viral load

Some studies supported the notion that being infected with a higher load of SARS-CoV-2 and having a higher load of the virus during infection is associated with more severe illness and even death [81–83]. The SARS-CoV-2 viral load (RNAaemia) is associated with cytokine storm, perhaps useful to predict the poor prognosis of COVID-19 patients [81]. Hence, higher viral load may result in more organ damage and disability in critically ill patients due to the stimulated cytokine storm and proinflammatory and inflammatory cytokines [81,84]. Moreover, patients with severe COVID-19 tend to have a high viral load and a long virus-shedding period [82]. High virus load promotes a robust immune response, which could contribute to a more severe clinical disease phenotype caused by cytokine storm [85]. While the viral load is necessary to trigger the illness, although variable in individual cases, the clinical course and severity depend on the magnitude of the airways' immune and inflammatory response.

3.3. Coinfections

The respiratory environment is not sterile, and coinfection with other viruses and bacteria may impact the pathogenesis and severity of SARS-CoV-2 infection, perhaps by interacting with the virus and altering the immune system [86]. For instance, SARS-CoV-2 and influenza A virus's coinfection have been reported, requiring more evaluation [87]. Another study reported that the most common coinfections detected in specimens from multiple sites in northern California were rhinovirus/enterovirus, respiratory syncytial virus, and non-SARS-CoV-2 Coronaviridae, respectively [88]. Coinfection among respiratory viruses is common in hospitalized patients, but it is unclear whether it contributes to more severe disease or not and requires more investigations [89].

Additionally, the impact of the commensal microbiome on the severity of the disease needs to be more scrutinized [90]. Notably, the microbial metabolic processes in the gut influence the production of cytokines. As there is a pivotal role of the immune system, especially cytokines in SARS-CoV-2 pathogenesis, the microbiome interactions with SARS-CoV-2 could be relevant to the microbiomes' impacts on cytokines [90].

It is speculated that prior exposure to other coronaviruses could confer partial immunity to SARS-CoV-2 [91]. Indeed, several studies suggest a significant amount of cross-reactivity and antibody production among different coronavirus infections. In this case, common cold coronaviruses (CCCs) have been suggested as the origin of SARS-CoV-2 specific T and B cells in unexposed individuals [92]. Therefore, the acquired immunity is expected to act preventively against more severe disease. However, although there is no direct evidence to support, the possibility of detrimental pre-existing immunity due to mechanisms such as original antigenic sin, which results in the propensity to elicit potentially inferior immune responses, and antibody-mediated disease enhancement should not be undermined [92,93].

4. Environmental factors

Among factors that directly affect the disease susceptibility and severity, the effect of environmental factors is also remarkable. However, it is still unclear whether environmental factors such as climate, air pollution, dietary, socio-economics, and culture are related to a more complicated disease phenotype. Environmental factors are very complicated, and it is hard to speculate how these factors affect the COVID-19 outcome.

4.1. Climate

Climate factors such as temperature and humidity may be necessary for endemic infections. Based on previous studies, droplet-mediated viral diseases like influenza are hypothesized to survive and spread more easily in cold and dry environments [94,95]. However, the role of temperature and humidity in the transmission of SARS-CoV-2 currently is not conclusive [96,97]. Reports from several studies indicate that temperature, humidity, and wind speed are inversely associated with the incidence rate of COVID-19 and deaths, which is consistent with influenza and SARS-CoV [72,95,97–100]. On the other hand, a positive correlation between precipitation and SARS-CoV-2 infections is also reported [101]. Rationally, changes in weather alone will not necessarily lead to declines in case counts without the implementation of extensive public health interventions.

4.2. Air pollution

Air pollution is another environment-related health threat to people who are more endangered by respiratory diseases. Results from a study suggest that long-term exposure to air pollution increases susceptibility to the severe outcomes of COVID-19 [102]. Patients in areas with higher air pollution levels before the pandemic are at greater risk than patients who are exposed to a cleaner air, comparatively [102]. As pollution impairs the first line of defense of upper airways, namely cilia [103], patients living in an area with high levels of pollutants are more prone to develop chronic respiratory conditions and are more vulnerable to any infections. Extended exposure to air pollution leads to a chronic inflammatory stimulus, even in young and healthy subjects [104]. Moreover, it is suggested that SARS-CoV-2 can survive longer when attached to a pollutant [105], and ACE2 expression increases due to exposure to air pollution [106].

4.3. Dietary

Diet might also be another independent risk factor in the development of severe infection. It is crucial to consume healthy, fresh, and nutritive foods and avoid diets including saturated fats, sugars, and refined carbohydrates, contributing to obesity and type 2 diabetes [107]. Although these products are not proven to be precisely concerning COVID-19, consumption of the above-mentioned products leads to chronic inflammation and impairs host defense against viruses due to the activation of the innate immune system and the impairment of adaptive immunity [108]. On the other hand, the routine dietary habits of people in some countries may lead to potent antioxidant or anti ACE activity. For example, eating uncooked or fermented cabbage by people living in low-death rate European countries, Korea and Taiwan, might be considered as a reason for the low prevalence of deaths by COVID-19 [109]. Adequate nutrient compounds such as vitamins and minerals are essential for the body to invigorate the immune system and avoid undesirable outcomes of infections [110].

Vitamin D deficiency is a general health issue in many regions. Its deficiency links to the development and progression of several comorbidities and susceptibility to infectious diseases. Vitamin D plays a vital role in modulating innate and adaptive immune responses [111,112]. It is reported that vitamin D insufficiency is highly prevalent in severe COVID-19 patients [96]. There is also a relationship between vitamin D consumption and reduced risk of COVID-19 and influenza infection [113]. Importantly, vitamin D consumption could be beneficial in COVID-19 due to its enhancing effects on regulatory T cell (Treg) levels [114,115].

Vitamin C is one of the most important sources of antioxidants [116]. Since the cytokine storm increases oxidative stress in patients suffering from COVID-19, vitamin C may be useful to reduce ARDS associated with COVID-19 [117]. Notably, it is reported that high-dose of oral vitamin C has antiviral effects with no significant side effects [118,119]. Therefore, the more vulnerable individuals would better consume high doses of vitamin C as a preventative measure in their daily diet [31,120].

Researchers have demonstrated that the level of iron in serum may have a close relation with COVID-19 severity and mortality rate since patients who died during hospitalization had significantly lower serum iron levels in comparison to those who recovered before and after the treatment. Noteworthy, patients with a low level of iron have cough as a common clinical presentation [98]. Therefore, iron consumption could be beneficial by decreasing chronic cough hyper-responsiveness and allergic inflammation in the lungs [121,122]. Also, there is data that Zinc consumption could limit the cytokine storm in COVID-19 due to anti-inflammatory activity [123].

4.4. Socio-economic

Socioeconomically, poor nutritional status is generally influenced by poverty and could be enumerated as a significant risk factor for the disease severity. In a study, people from Asia and black-colored skin people were shown to have a higher risk of death from COVID-19, partially attributed to deprivation as a significant problem [124]. Besides, Hispanics and indigenous communities of Latin America may have been facing the pandemic more vulnerably due to the deprivation and social disparities [125,126]. Also, the health care system's inefficiency in low- and middle-income countries dramatically increases the impact of COVID-19 [126]. Notably, there is evidence of more virus transmission in crowded areas [127]. For example, many cases of COVID-19 in the U.S. have occurred among older adults living in nursing homes or Long-term homecare facilities [128]. Occupational risks for getting a severe disease are also notable. Essential workers in healthcare, social care, sanitary services, and transportation simply cannot work from home due to their job's characteristics. Therefore, these groups are more likely to be exposed to the virus, potentially putting them in the high-risk group [129].

4.5. Culture

Different populations with different cultures and traditions are not expected to respond similarly to the outbreak. People with a culture of being more socially distant are less prone to spread the virus [130]. Controlling measures have been taken by countries in many areas, including healthcare services, work arrangements, the economy, and educational institutions. Beforehand, early enacted strict social distancing and stay-at-home policies in some countries have shown to play crucial roles in controlling the outbreak [130]. Supplying masks and gloves, as well as testing kits and treatment services, have been considered among the highest priorities. However, currently, it is recommended to wear gloves only while caring for sick individuals, which is most relevant to health care workers. The unessential use of gloves provides a false sense of security and may increase the virus spread [131]. Besides, many countries have provided various financial supports for the needy strengthening social solidarity during the pandemic. Furthermore, several online education options have been implemented following school closures. Identifying environmental risk factors will affect vaccine policy and further educate families and health personnel about these risk factors. (see Fig. 1).

5. Discussion

While everyone may be sensitive to SARS-CoV-2 infection, the nature and severity of the disease vary among individuals. The virus is widespread in many countries worldwide, but only a small number are severely affected by COVID-19. As such, severe disease and death occurs only in a small subset of infected cases. Investigation of factors that could determine the clinical course and outcome of the disease appears

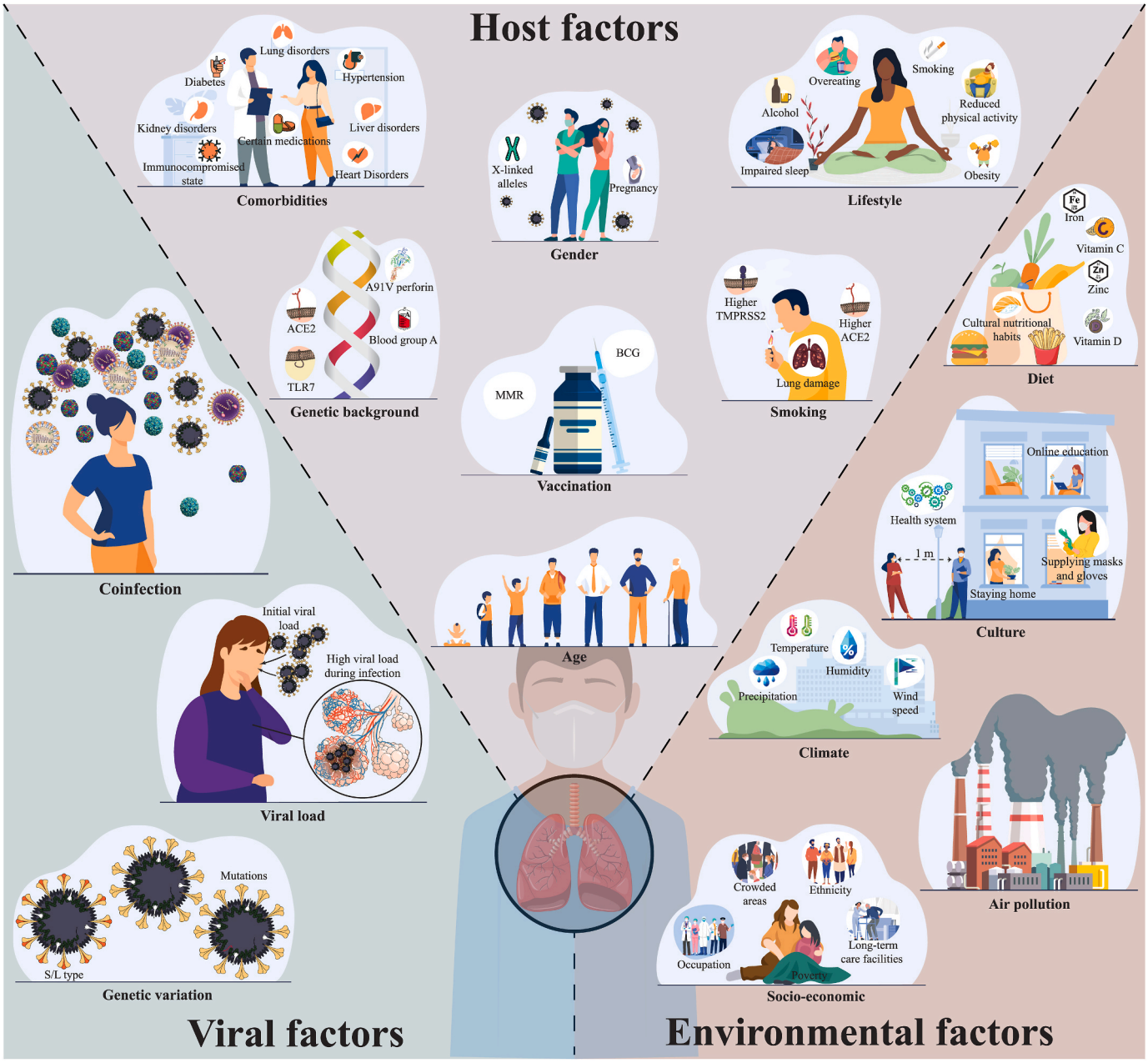

Fig. 1. Factors affecting the COVID-19 outcome. There are many suggested host, viral, and environmental factors contributing to the COVID-19 phenotype. The severity of COVID-19 probably depends on the varying degrees of interaction among host, viral, and environmental factors. Interactions among these factors lead to differences in inflammatory and immune responses in the lung and different courses of the disease.

to be intriguing among scientists. Since the COVID-19 situation is rapidly changing, finding specific factors associated with complicated disease outcome is very demanding. Although our knowledge of the virus pathogenesis and behavior is not advanced enough to predict disease outcomes, studies on similar viruses have provided some critical insights. Since the development of effective treatment and vaccine is still ongoing, there is a huge possibility that we have to live with SARS-CoV-2 for a long time and thus, the better understanding of the factors associated with the severity of the disease is essential.

The exact role of factors for complex COVID-19 phenotype remains contentious. Host differences could indeed dictate the clinical response to any viral infection. People are different in many aspects, especially in genetic makeup. Genetic differences are well-known to contribute to individual variations in the immune response to pathogens such as respiratory viruses. However, the characterization of stimulating genes for this complex disease remains unclear. Exploring host-related differences is vital in identifying high-risk individuals and will provide valuable information and basics for personalized medicine. Importantly, in emergency conditions, vaccines or drugs could be administered to more susceptible groups of people. The potential risk of SARS-CoV-2 mutation or the evolvement of its virulence activities during the pandemic is a vital question that might change all future research and disease management in this regard. Although the virus pathogenesis has not yet been fully understood in detail, it seems that viral load is necessary to drive acute disease. However, the outcome depends on the level of the immune and inflammatory responses in the airway. Discovering a relationship between viral factors and clinical consequences of COVID-19 may be meaningful in the future development of vaccines and treatments. Environmental factors affect the COVID-19 course by the virus epidemiology alteration, transmission rate and population's immune statues. Significantly, the effect of environmental factors varies in regions with different climate patterns, cultures, traditions, and many other interfering factors. Understanding the environmental factors associated with a severe clinical course is likely to help develop an evidence base to inform vaccine policy, particularly in developing countries.

6. Conclusion

The COVID-19 outcome highly depends on a complicated interaction between the host, virus, and environment, which affects the intensity of the host response and leads to different clinical courses of the disease. Therefore, further studies, particularly in the context of the host, viral, and environmental factors, are required. More investigation is needed to focus on how the virus interacts with the host and environment, leading to the wide variance in observed symptoms.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Authors' contributions

AT conceptualized and designed the study. SS and MM collected data and drafted the manuscript. AT, VS, AT, and AM evaluated and edited the manuscript. MR depicted the manuscript in Fig. 1. All authors have read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2; Coronavirus disease 2019, COVID-19; Chronic obstructive pulmonary disease, COPD; NLR Family Pyrin Domain Containing 3, NLRP3; Acute respiratory distress syndrome, ARDS; Angiotensin-converting enzyme 2, TMPRSS2; Bacillus Calmette-Guérin, BCG; Measles-Mumps-Rubella, MMR; Common cold coronaviruses, CCCs; Angiotensin-converting enzyme inhibitors, ACEIs; Toll-like receptor 7, TLR7; Interferon, IFN; Regulatory T cell, Treg.

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