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PERSPECTIVE

Immune-epidemiological parameters of the novel coronavirus – a perspective

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ABSTRACT

Introduction: At the end of 2019, Wuhan, a city in China with a population of about 11 million, witnessed the outbreak of unusual pneumonia. As of 29 March 2020, the disease has spread to more 199 countries and territories worldwide. The 2019 novel coronavirus, 2019-nCoV, is known as the probable causative agent of the illness.

Areas covered: Here, the epidemiological dynamics of the coronavirus disease 2019 (COVID-19) that stand in close relation to distinct immunogenetic characters of the pathogen are discussed, to understand the ability and inability of the immune system in combatting COVID-19.

Expert opinion: The elderly population is at increased risk of developing and dying from COVID-19. Comorbidity is present in more than 30% of cases with COVID-19. Except for less than 1% of the total, a chronic condition has been found in all cases that died from COVID-19. Men are more than 1.5 times more likely to die from COVID-19. Evidence links aging to cytokine dysregulation and T-cell repertoire reduction, male population to relatively reduced anti-viral immunity, and COVID-19-related comorbidities to hyper inflammation. The transmission of COVID-19 is influenced by the host-related factors that are known to be associated with immune dysregulation.

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1. Introduction

The 2019 novel coronavirus (2019-nCoV; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) emerged after six other human coronaviruses. Four common human coronaviruses that cause mild to moderate upper respiratory tract illnesses, including 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), and HKU1 (beta coronavirus), were first recorded in the 1960 s. Two other human coronaviruses are SARS-CoV and MERS-CoV, which lead to severe lung infections known as severe acute respiratory syndrome – SARS and the Middle East respiratory syndrome – MERS, respectively [1,2]. The SARS-CoV outbreak occurred in 2002, starting in China and spreading to other countries, with a death rate of 11%. The MERS-CoV outbreak occurred in 2012, starting in Saudi Arabia and spreading to other countries, with a death rate of 37%. Now, we are seeing the outbreak of 2019-nCoV, which can affect both upper respiratory and lower respiratory tracts and causes unusual viral pneumonia, named coronavirus disease 2019 (COVID-19) or novel coronavirus-infected pneumonia (NCIP). All of the three coronaviruses that have caused human pandemics are of beta coronaviruses.

2. A brief abstract of anti-viral immunity

Anti-viral immunity includes both innate immune and adaptive immune responses. The two main varieties of innate immune receptors, transmembrane and cytosolic, are critical to establishing the innate immune responses, thereby leading to adaptive immune responses. Transmembrane receptors, mainly toll-like receptors (TLRs), can sense both live and dead viruses. The capacity of cytosolic innate immune receptors, including RIG-I-like receptors (RLRs), Nod-like receptors (NLRs), and AIM2-like receptors (ALRs), is limited, as they can only sense live viruses [3]. Consistently, among different innate immune receptors, TLRs are most closely related to adaptive immune responses. TLRs are, therefore, an important element of anti-viral immunity. They can detect both the complete (infectious) viral particles, including viral nucleic acid and viral envelop proteins, and defective viral particles [4]. Upon recognition of a virus, TLR signaling upregulates the expression of pro-inflammatory cytokines and costimulatory molecules, through the accumulation of interferons (IFNs) [5]. Consequently, adaptive antimicrobial immunity is processed by costimulatory molecules.

2. 1. *SARS-CoV says: stop signal boosting interferons and pro-inflammatory cytokines*

To date, no experiment has proven which innate immune receptors undertake the detection of SARS-CoV. Patients with severe SARS-CoV infection show the aberration of the innate immune system [6]. In particular, the induction of pro-inflammatory cytokine, type I IFNs, and interferon-stimulated

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Article highlights

- Tracing the epidemiological character of COVID-19 provides an understanding of the immunity of the disease.
- The elderly population is at increased risk of developing and dying from COVID-19.
- Comorbidity is present in more than 30% of cases infected with COVID-19.
- Men are more than 1.5 times more likely to die from COVID-19.
- The transmission of COVID-19 is influenced by the host-related factors, e.g., aging, male gender, and comorbid conditions, known to be associated with immune dysregulation.
- The first and ultimate picture of COVID-19 is a lung injury accompanied by the storm of pro-inflammatory cytokines.

genes (ISGs) would undergo oscillations that are clearly favorable to SARS-CoV.

The release of pro-inflammatory cytokines and chemokines occurs on the first day of infection. High levels of pro-inflammatory cytokines in patients with SARS-CoV disease correlate with acute respiratory distress syndrome in aged animals [6].

The upregulation of type I IFNs and ISGs is not observed until two days after infection. Studies show that IFN deficiency does not exacerbate SARS-CoV disease in animals, while treatment with type I IFNs could help control SARS-CoV replication. Therefore, it is possible to suppose other innate immune mechanisms, which will have an essential role in immunity against SARS-CoV [6].

2. 2. Certain T-cell population subset develop the storm of cytokines during initial stages of COVID-19

Microparasites are living organisms smaller than parasites that reproduce in a single host, thereby resulting in the host-mediated immune responses. Macroparasites are bigger and can have multiple hosts. The 2019-nCoV involves cytokines and chemokines from the initiation to the elongation phases of the disease [7]. In its initiation stage, the 2019-nCoV would increase plasma concentrations of different cytokines, including IL-1β, IL-1Rα, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and vascular endothelial growth factor [7]. Critically ill patients admitted to the intensive care unit (ICU) showed higher levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα compared with those who did not need to be in an ICU [7]. The work of 2019-nCoV seems to be an interplay between different T-helper (Th) cell population subsets, e.g., Th1, Th2, and Treg. There are instances, in both microparasites and macroparasites, which have been correlated with such this orchestration of immune responses. *Mycobacterium tuberculosis* is a prototype of microparasites linked to all three Th1, Th2, and Treg cell expansion [8].

2. 3. Eventually, the 2019-nCoV would downregulate the immune system

Among patients presenting in primary care with clinical symptoms of illness, the prevalence of dyspnea and acute respiratory distress syndrome is about 51% and 27% at the median of 8 and 9 days from illness onset, with about 40% requiring ICU at the median of 10.5 days from illness onset. A study of 12 patients infected with the 2019-nCoV revealed abnormalities in the plasma content of biochemical and immune parameters [9]. Of note, blood abnormalities, including hypoalbuminemia, the low number of lymphocytes, low percent of neutrophils, and high level of lactate dehydrogenase (LDH), Angiotensin II, and C-reactive protein (CRP), were associated with the severity of lung injury.

3. The 2019-nCoV: a virus that destroys equilibrium in the respiratory tract

In the case of viral respiratory infection, the process, through which the immune system can continually recognize viral particles and seek to eliminate infected cells, takes place with difficulty. This is partly because the respiratory tract with an extensive mucosal surface area, and its exposure to the environment has everything favorable for microbial colonization and surveillance; and partly because of the nature of virus, that is pathogenic more than bacteria, and its power of attachment to the mucosal surface and to interact with it; so that the respiratory epithelium will be liable to superinfection, and this is what occurred with the Spanish flu pandemic in 1918–1919 [10]. Hence, it would be understandable that the presence of a virus by which it increases bacterial adherence, interferes with the epithelium barrier integrity, induces production of adhesion proteins and viral factors, and downregulates the function of immune cells, destroys the equilibrium of the respiratory system [10].

4. The 2019-nCoV: a microparasite that poses a new problem for epidemiology

Besides the respiratory system, coronaviruses will tend to affect the nervous system and gastrointestinal system in animals [11–13]. On the evidence of having been transmitted from animals to humans (zoonotic diseases), all three coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV are correlated with an aggressive form of the disease. The transmission of the 2019-nCoV to humans occurs directly and indirectly. It mainly occurs through a direct transmission of respiratory droplets. Indirect transmission that happens through touching surfaces contaminated with the virus is a less possible source of spread [14].

The 2019-nCoV spreads during the clinical latency stage, and therefore, classical models for epidemic outbreaks do not apply to the particular case of 2019-nCoV. Also, an average reproductive number of 3.11 indicates that the average number of secondary cases with the 2019-nCoV is increasing [15]. The official data estimate that the average clinical latency stage lasts 7 days or more and it is longer than the median incubation period of 5.2 days (2–14 days) [15]. Thus, there is a promising point that the treatment of symptomatic individuals can be useful. However, it should be mentioned that the reproduction number varies over time depending on the estimation models. The average reproduction number estimated by stochastic methods, mathematical methods, and

exponential growth are 2.44, 4.2, and 2.67, respectively [16]. Moreover, simulation methods predict that with continuing efforts Wuhan would achieve a reproduction number of less than one soon [17]. Here, we frame immunogenetic explanations for the epidemiological dynamics of COVID-19.

5. The 2019-nCoV is coming from a cold low humidity environment

Wuhan, where the condition of 2019-nCoV first appeared, has experienced the worst drought year of the last 40 years. Additionally, December, when 2019-nCoV first recognized, is the first month of winter. Both with time and place, the outbreak of SARS-CoV occurred in precisely the same condition (during the winter season and in low humidity). We can, therefore, understand the relation between the origin of the 2019-nCoV and the changing condition of climate.

Both winter and low humidity act as a stressor for the immune system. Evidence indicates the association of cold temperature and low humidity with respiratory tract infections in the manner that the lower the environmental temperature/humidity, the more and the sooner respiratory tract infections occur in a population [18]. Early interferon-gamma (IFN-γ) induction in viral infections indicates a battle between the innate immunity and the virus. In colder temperature, IFN-γ production by the RIG-I-like receptors (RLRs) that are essential for the recognition of viral RNA by the innate immunity decreases in airway cells, so well adapted for viral replication [19]. Then, the immune system would commence fever, to allow the expression of the TLR4, and trigger from this a series of anti-viral immune responses characterized by the production of cytokines [20]. With nearly 99% reporting, the most common symptom of 2019-nCoV infection at onset is fever.

6. The infectivity of 2019-nCoV depends on the host-related factors

The impact of the host-related factors, age, gender, and physiological health, is evident in the transmission of 2019-nCoV as well.

6. 1. The elderly population is at increased risk of developing and dying from COVID-19

The mean age of people with COVID-19 is 52.4 years [21]. Age could strongly predict the fate of 2019-nCoV disease. 56-year-old became the youngest patient with severe COVID-19. By contrast, children and adolescents are the least likely group to be infected with the 2019-nCoV, occurring in only 2% of patients 19 years of age or younger. Even if they get sick, they will get a mild form of disease without serious complications, with an average probability of 0.2% of dying. A study of 9 infants with the 2019-nCoV infection reported fever and mild upper respiratory tract symptoms as the only symptoms of the virus [22].

One of the most remarkable features of anti-viral immunity is that it shows adaptation in its strategy to the stages of human life. The innate immune cells are born capable of making T regulatory cell cytokine (interleukin-10 (IL-10)) and T helper 17 (TH17) cell cytokines (IL-6 and IL-23), but incapable of induction of T helper 1 (TH1) cell cytokines (type I interferons, IFN-γ, and IL-12) [23]. The diversity of the T-cell receptor (TCR) repertoire decreases with age, while a new lineage of oligoclonal T cells that express natural killer (NK)-related receptors (NKR) is formed [24].

Taken together, the real-time data of the 2019-nCoV infection in addition to the experimental evidence regarding those immunological features which are prominent in neonates and children more than in adults, it seems that the importance of the immunomodulatory cytokine IL-10 should be exaggerated in anti-2019-nCoV immunity. Moreover, aging is a condition associated with inflammation, whereas the neonatal period related to an immature anti-inflammatory response. Considering the pro-inflammatory response as the initiator of SARS-CoV infection, there is a logical possibility in an overwhelming inflammatory reaction in the aged subjects. Supporting this, old animals with SARS-CoV infection show high levels of pro-inflammatory cytokines conjointly with the signs and symptoms of respiratory failure [6].

6. 2. Men are more likely to be the target of COVID-19

Men constitute more than two-thirds of the reported cases (73% vs. 27%) [7]. Also, men are more than 1.5 times more likely to die from COVID-19 (death rate: 2.8% vs. 1.7%).

Generally, sexual differences play an important role in affecting the immune system function, and in therefore driving variability in response to infections. In particular, men are generally thought to produce a lesser amount of type I IFNs and inflammatory cytokines and possess a lower number of circulating T cells [25]. All that is expected to be required for the defense against viruses has been deficient in men compared to women. This distinction between the anti-viral immunity of men and women exists due to the genetic factors, environmental factors, and hormonal factors.

6. 3. Comorbidities are noted in most COVID-19-related deaths

Comorbidity is present in more than 30% of cases with COVID-19 [7]. Except for less than 1% of the total, a chronic condition has been found in all cases that died from COVID-19. Arranged by their related mortality rates, the chronic conditions in the victims of the virus include cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer. All these conditions in the long-term tend to make the immune system imperfect in both innate and adaptive immune functions [26].

The renin-angiotensin system (RAS) is detectable in several tissues and serves as a hormone system and contributes to the regulation of blood pressure through the generation of autocrine or paracrine signals. The RAS and its key player, angiotensin-converting enzyme 2 (ACE2), have been implicated in cardiovascular diseases through mediating inflammation [27]. 2019-nCoV binds to the ACE2 receptor. Therefore, we might expect that 2019-nCoV poses a significant threat to patients, who on their own, already have problems in the RAS, and it would be partly because the process of inflammation takes place more than before infection occurs.

7. The virulence of 2019-nCoV

Viruses in the family of *Coronaviridae* vary in a remarkable degree to become genetically mutated, though they all share the genetic mutability by recombination mechanism and error-prone replication – a fundamental mechanism of genomic variation and virulence. Using this mechanism, SARS-CoV became mutated and increased its virulence, whereas MERS-CoV has not changed significantly from its discovery in 2012 [28]. The former binds to angiotensin-converting enzyme 2 (ACE2) and the latter to the CD26 receptor [28]. ACE2 receptor appears to be the cellular receptor for the 2019-nCoV, as well as for CoV-NL63, which results in a mild to moderate lung disease. Taken together, binding the same receptor would not necessarily pertain to the same behavior by SARS-CoV and 2019-nCoV.

8. The pathogenicity of 2019-nCoV

The pathogenicity of the disease seems to be associated with its transmissibility in terms of the more the reproductive number, the less the severity of the disease. The 2019-nCoV with the overall case fatality rate of 4.65% as of 29 March 2020 and the reproduction number greater than one would probably exhibit a trend similar to that of H1N1 in 1918 [28].

9. The 2019-nCoV and other extremely virulent coronaviruses have inherited from a common ancestor

Phylogenetic analysis indicates a common ancestor to which human 2019-nCoV, human SARS-CoV, and the bat SARS-CoV converge. Additionally, the four structural viral proteins, spike (S), membrane (M), nucleocapsid (N), and envelope (E), imply a high degree of shared identity in range 97.7-100% between the human and bat coronaviruses [29]. It supports the view that the human 2019-nCoV is descended from an animal.

10. The 2019-nCoV has acquired differences marked by the protein S and T-cell epitopes

10. 1. The receptor-binding motif of 2019-nCoV has undergone modification

SARS-CoV and 2019-nCoV enter the cell in the same way – through binding ACE2, which is present in lung and gastrointestinal epithelia [30]. However, poor conservation of the receptor-binding motif of 2019-nCoV, known as the structural protein Spike (S), with that of SARS-CoV indicates that this new protein has undergone modification [31]. When compared with the Spike gene of a marine coronavirus and a bat coronavirus, the Spike gene of the human 2019-nCoV varies at different points due to both synonymous mutations and non-synonymous substitutions [29]. The varieties partly explain that the human 2019-nCoV has adopted a new structure to become fitted for attachment to the human cells.

10. 2. T-cell epitopes of this new strain are different from those of other aggressive coronaviruses

The three extremely virulent strains, 2019-nCoV, MERS-CoV, and SARS-CoV, show similar profiles of B-cell epitopes. However, the novel coronavirus exhibits a distinct pattern of T-cell epitopes. In particular, CD8 T-cell epitopes, which are mainly engaged in anti-viral immunity, appear to have mutated more frequently in 2019-nCoV than those of CD4 T-cell epitopes in MERS-CoV and SARS-CoV [31].

11. Expert opinion

COVID-19 is a life-threatening living challenge for both epidemiology and immunology. The current evidence points out the effect of this novel coronavirus on inhibition of anti-viral immune responses and, therefore, its powerful capacity for replication in the host cells. On the other hand, COVID-19 has shown the highest incidence rate and mortality rate in the elderly population and people with certain comorbidities who are known to have differences in their immune profile. The review concludes that tracing the epidemiological character of the virus provides an understanding of the immunity of the disease. It can help with the prevention and treatment of the disease in the most vulnerable individuals.

No specific drug exists for COVID-19. However, patients can be given a variety of medicines and supplementations that improve immune responses, including metformin, glitazones, fibrates, sartans, and atorvastin. Also, there is a long list of a less safe but better choice in terms of anti-viral immunity to provide to the patients, e.g., cyclosporine, lopinavir-ritonavir, interferon beta, ribavirin, monoclonal antibodies, and anti-viral peptides. An *in vitro* study testing the effects of seven drugs on the infection rate of the COVID-19 reported that chloroquine, an anti-malarial agent, and remdesivir, an anti-Ebola drug, effectively inhibited the 2019-nCoV infection [32]. It was strengthened by evidence that remdesivir was successful in both preventing and controlling MERS-CoV-induced clinical disease in nonhuman primates [33]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are apparently required for the normalization of the abnormally high level of Angiotensin II patients with COVID-19 [9]. However, no consensus has yet been reached about the use of ACEI and ARB in patients with COVID-19 [34]. The other challenge is that whereas the 2019-nCoV is isolated from the host and grown in host cells, there is no animal model of disease to judge the condition is caused by 2019-nCoV [35]. All the propositions need testing in an animal model of disease before human use.

No doubt, a future line of research should be devoted to the development of vaccines for active immunization against 2019-nCoV. The viral genome and its structural proteins have a direct tendency to impair immune surveillance. As the analysis of protein sequences has shown, eight HLA-DR epitopes that are located in the Spike, Envelope, and Membrane of the 2019-nCoV play an essential part in the obstruction of the immune surveillance [29]. Also, there are B-cell and cytotoxic T lymphocyte epitopes that are uniquely present on the surface glycoprotein of 2019-nCoV [36]. These epitopes are likely a vaccine target for the 2019-nCoV. Superinfection with an

apathogenic dsRNA virus strengthens the upregulation of IFNs, which are the key player of anti-viral immunity [37]. It could be shown that this method, called the superinfection therapeutic (SIT) strategy, promotes the resolution of viral infections, both DNA and RNA viruses [38]. However, this does not determine whether it would confer a benefit in the case of 2019-nCoV as well. Another era in the treatment of infection with 2019-nCoV can be devoted to the clinical development of T-cell products.

The first and ultimate picture of COVID-19 is a lung injury accompanied by a storm of pro-inflammatory cytokines. However, the use of anti-inflammatory drugs, e.g., corticosteroids, has its own adverse side-effects and more importantly, as demonstrated by a few avalabe studies [39–41], its effects on the clinical endpoints seem to be not more than standard anti-viral agents plus supportive care. Finding immune biomarkers that can distinguish severe-to-critical from mild-to-moderate infection would help to designate targets for immunotherapy of COVID-19.

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