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Reviews

COVID-19: the first pandemic of the 21th century. A review of the literature

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Abstract

The new coronavirus SARS-CoV-2 (COVID-19) was recognized in December 2019 as a cause of severe pneumonia and has now led to a global pandemic [1, 2]. Respiratory illnesses caused by COVID-19 cover a whole range of severities. Identifying the risk factors and protective factors for the severity of COVID-19 disease is essential to direct the development of new treatments and infection prevention strategies. The first large series of cases identified several risk factors for severe forms of the disease, including advanced age, hypertension, diabetes, cardiovascular disease, exposure to tobacco, and obstructive pulmonary chronic disease [1, 3].

The Chinese Center for Disease Control and Prevention published a significant case series study of coronavirus disease 2019 (COVID-19) (72 314 cases, updated through February 11, 2020) [4, 5]. The authors of this paper summarized key findings from this report and discussed emerging understanding of and conclusions from the COVID-19 epidemic.

Keywords: *COVID-19 infection, the diagnosis, mutations, vaccines*

Concerning the epidemiologic characteristics of the COVID-19 outbreak, among a total of 72 314 case records, 62% were classified as confirmed cases of COVID-19. The diagnosis was based on a positive viral nucleic acid test result from throat swab samples. In 22% of cases, the diagnosis was based on symptoms and history of exposures only, without any test being made because testing capacity was insufficient to meet current needs. In 15% of cases, without performing the viral nucleic acid test, the diagnosis was made based on symptoms, exposures, and lung imaging features consistent with coronavirus pneumonia. In only 1% of patients, the diagnosis relied on a positive viral nucleic acid test result but lacking typical symptoms, including fever, dry cough, and fatigue [4, 5].

Most cases were diagnosed in Hubei Province (75%), and most reported Wuhan-related exposures (86%; i.e., Wuhan resident or visitor or close contact with Wuhan resident or visitor). Most cases were classified as mild (81%; i.e., non-pneumonia and mild pneumonia). However, 14% of cases were severe (i.e., dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure) [4, 5].

The overall case-fatality rate (CFR) was 2.3% (1023 deaths among 44 672 confirmed cases). No deaths were reported among mild and severe cases. The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions. 3.8% of the cases were health workers; 14.8% of confirmed cases among health workers were classified

as severe or critical, and five deaths were observed [4, 5].

COVID-19 rapidly spread from a single city to the entire country in just 30 days. Epidemic curves reflect what may be a mixed outbreak pattern, with early cases suggestive of a continuous common source and later cases showed the virus beginning to display transmission from person to person [4, 5].

Although many articles, published until July 2020, had established the clinical characteristics of patients with COVID-19 [2, 3, 6, 7, 8], details of an allergic nature and information on the Laboratory results concerning these allergic diseases are patients have not yet been reported. Previous studies have addressed the possible relationship between viral infections, immune response, allergy, and asthma. Several types of viruses, such as rhinovirus (RV) and respiratory syncytial virus (RSV), have been at the center of research [6, 9, 10, 11, 12, 13], while for the coronavirus, and in particular for COVID-19, there is no connection in this context.

It is generally established that the existence of an allergic field can increase the risk of virus-induced exacerbation of allergic diseases such as asthma [6, 14, 15]. Genetic predisposition, deficient antiviral response, impaired function of immune cells, damage to the epithelium, and response by cytokines and chemokines may contribute to the synergistic development of the exacerbation of the allergic disease both by the allergen than by the virus, concerning particularly allergic troubles affecting the respiratory tract [6, 16, 17, 18]. However, respiratory infections early in life may play a protective role against the development of Th2-mediated allergic disease [6, 19].

The prevalence of chronic obstructive pulmonary disease (COPD) in people aged ≥ 40 years was 13.7% in China, according to a recent study [22]. Viral respiratory infection is a common trigger for COPD exacerbation [23]. The prevalence of SARS-CoV-2 infection in patients with COPD is unclear. This research [6] aims to study the clinical and laboratory characteristics of hospitalized COVID-19 patients, including the differences between severe and non-severe patients, and reveal the relationship between SARS-CoV-2 infection, immune response, allergy, and clinical manifestations, focusing on asthma, COPD, and smoking.

In the above study, pharyngeal swabs from patients were collected for detection of SARS-CoV-2 viral nucleic acid using the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay. The detailed protocol has already been described [6, 7].

Medical laboratory tests from samples collected from each patient included:

- the leukocytes, lymphocytes, and eosinophils count;
- the percentages of lymphocytes and eosinophils;
- the concentrations of D-dimers, C-reactive protein (CRP), procalcitonin (PCT), serum amyloid A (SAA), and serum creatine kinase,
- as well as the detection of various pathogens (including Mycoplasma pneumoniae, Chlamydia pneumoniae, influenza A virus, influenza B virus, parainfluenza, group B coxsackievirus, adenovirus, echovirus, respiratory syncytial virus, Epstein-Barr virus, and cytomegalovirus).

Because no patient had a history of direct exposure in the Huanan Wet Market or the Wild Animal Market, the authors assumed that all patients in this study were community-infected cases.

Only two patients with COPD (chronic obstructive pulmonary disease) were identified. Sixteen patients had a self-reported medical history of drug hypersensitivity, the drugs involved being penicillin, cephalosporins, and specific Chinese traditional medicines. Two patients reported chronic urticaria. No other self-reported allergic diseases (including asthma, allergic rhinitis, food allergy, atopic dermatitis, and other type-2 allergic diseases) have been reported.

In summary, this study [6] highlighted the clinical and laboratory characteristics of 140 patients infected with COVID-19 in the community, showing a female-to-male ratio of approximately 1: 1. A low prevalence of smokers and the absence of allergic disease, except for drug hypersensitivity and urticaria, self-reported by all patients, seemed to indicate that allergic disease and a history of smoking may not be susceptibility factors for COVID -19. The positive correlation between the number of eosinophils and blood lymphocytes suggests that eosinopenia associated with lymphopenia may be a valuable indicator for diagnosing COVID-19 in patients with typical symptoms and radiological changes.

Another study concerning the association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2 was also published in July 2020 [1]. In the authors' opinion, identifying the risk factors and the protective ones for the severity of COVID-19 disease is essential to direct the development of new treatments and infection prevention strategies [1, 20]. They hypothesized that a potential explanation for the unexpected observation that asthma and other allergic diseases might not represent a risk factor for severe COVID-19 disease is reduced expression of the gene encoding

ACE2 in the respiratory tract cells and, therefore, a decrease in the susceptibility to infection. To test this hypothesis, they investigated whether asthma and respiratory allergy are associated with reduced expression of ACE2 in airway cells from 3 different cohorts of children and adults. In all three studies, total RNA was extracted from nasal or lower airway epithelial brushing samples, with RNA sequencing being performed independently for each study, as previously described [1, 21].

Children at high risk for asthma, correlated with parental history, and living in urban neighborhoods, were enrolled before birth and followed prospectively in the Urban Environment and Childhood Asthma cohort (Urban Environment and Childhood Asthma - URECA); 318 of them had nasal epithelial brushings obtained at the age of 11. The study assessed the prevalence of asthma at the age of 10 years. The atopic status was defined by trajectories of allergic sensitization (none or minimal, low, medium, and high) as previously described [1, 22]. Additional type 2 biomarkers, including fractionated expired nitric oxide, peripheral blood eosinophils level, and total IgE level, were assessed using standard methods.

In URECA, allergic sensitization was inversely correlated to the expression of ACE2 in the nasal epithelium regardless of asthma clinical manifestations. The expression of ACE2 was also significantly inversely associated with type 2 biomarkers, including the number of positive results for allergen-specific IgE, total IgE level, fractionated expired nitrogen monoxide, and nasal epithelial expression of IL13 [1].

The team also evaluated 24 adult participants with allergic rhinitis to cat fur who had no symptoms of asthma in the previous year and who had been enrolled in a study in which they underwent a nasal challenge to cat allergens (nasal allergen challenge - NAC) and were exposed to a cat allergen via an environmental exposure chamber (EEC), as previously described [1, 21]. Nasal brushing samples, pre-and post-allergen provocation, were taken. Exposure to allergens via NAC and EEC led to significant reductions in ACE2 expression.

An additional cohort of 23 adult participants with mild asthma, not treated with asthma control therapy, were subjected to a segmental allergenic bronchial challenge to house dust mite, ragweed, or cat, as previously described [1, 23]. Pre- and post allergen challenge bronchial brushings were obtained and demonstrated a significantly reduced expression of ACE2 in the epithelium of the lower respiratory tract in post allergen challenge samples.

Starting from in vitro models, the authors of the same paper [1] evaluated the effects of IL-13, a type 2 cytokine strongly related to allergic asthma, on the expression of ACE2 in differentiated epithelial cells of the respiratory tract. IL-13 significantly reduced the expression of ACE2 in both nasal and bronchial epithelium.

In this article [1], the team of authors reports that respiratory allergy and controlled allergen exposures are each associated with significant reductions in ACE2 expression.

The most robust feature of the study consists of the carefully phenotyped cohorts of children and adults. In addition, the allergenic challenge studies included both upper and lower respiratory tract samples. Previous work suggests a direct association between ACE2 mRNA levels and ACE2 protein levels in the lung [1, 24]. Modulation of ACE2 expression by type 2 inflammatory processes suggests the need to comprehensively assess the role of type 2 immune regulation in the pathogenesis of COVID-19 [1].

And finally, because vaccination is the key to ending this pandemic, we will summarize a paper published by WHO in March 2021 concerning the effects of virus variants on COVID-19 vaccines [25]. This article is part of a series of explainers on vaccine development and distribution.

All viruses – including SARS-CoV-2, the virus that causes COVID-19 – evolve. When a virus replicates or makes copies of itself, it sometimes changes slightly, which is typical for a virus. These changes are called "mutations." A virus with one or more new mutations is "variant" of the original virus.

A widely circulating virus in the population and causing many infections also increases its mutagenicity. (The more opportunities a virus has to spread and replicate, the more chances it has to undergo mutations. - ! REDUNDANT)

Most viral mutations have little to no impact on the virus's ability to cause infections and disease. But depending on where the changes are located in the virus's genetic material, they may affect a virus's properties, such as transmission or severity.

The COVID-19 vaccines currently in development or approved are expected to provide at least some protection against new virus variants since these vaccines elicit a broad immune response involving a wide range of antibodies and cells. Therefore, changes or mutations in the virus should not make vaccines completely ineffective. If any of these vaccines prove to be less effective against one or more variants, it will be possible to change the composition of the vaccines to protect against these variants.

Data continues to be collected and analyzed on new variants of the COVID-19 virus. WHO is working with researchers, health officials, and scientists to understand how these variants affect virus behavior, including their impact on the vaccine's effectiveness, if any.

While we are learning more, we need to do everything possible to stop the virus's spread to prevent mutations that may reduce the efficacy of existing vaccines. In addition, manufacturers and the programs using the vaccines may have to adjust to the evolution of the COVID-19 virus: for example, vaccines may need to incorporate more than one strain when in development, booster shots may be required, and other vaccine changes may be needed.

WHO has been tracking mutations and variants since the start of the COVID-19 outbreak. Research groups have carried out genomic sequencing of the COVID-19 virus and shared these sequences on public databases. This global collaboration allows scientists to track better how the virus is changing. WHO recommends that all countries increase the COVID-19 virus sequencing wherever possible and share data to help each other monitor and respond to the evolving pandemic.

WHO has also established a SARS-CoV-2 Risk Monitoring and Evaluation Framework to identify, monitor, and assess concern variants. It will involve components like surveillance, research on variants of concern, and evaluation of the impact on diagnostics, therapeutics, and vaccines. The framework will guide manufacturers and countries on changes that may be necessary for COVID-19 vaccines.

To prevent future new variants of the COVID-19 virus, stopping the spread at the source remains critical. Current measures to reduce transmission include frequent hand washing, wearing a mask, physical distancing, good ventilation, and avoiding crowded places or closed settings. These measures continue to work against new variants by reducing the amount of viral transmission and reducing opportunities for the virus to mutate.

Scaling up vaccine manufacturing and rolling out vaccines as quickly and widely as possible will also be critical for protecting people before they are exposed to the virus and the risk of new variants. Priority should be given to vaccinating high-risk groups everywhere to maximize global protection against new variants and minimize the risk of transmission. Moreover, ensuring equitable access to COVID-19 vaccines is more critical than ever to address the evolving pandemic. As more people get vaccinated, we expect virus circulation to decrease, leading to fewer mutations. Vaccines are a critical tool in the battle against COVID-19, and there are clear public health and lifesaving benefits to using the tools we already have.

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