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IMMUNOPATHOGENETIC BASES OF SEVERITY OF COVID-19. LITERATURE REVIEW

Assiya A. Yessenbayeva[1], Zhanna B. Mussazhanova[2,3], Maksut S. Kazymov[1], Bakytbek A. Apsalikov[1], Dastan N. Saidualiev[1], Gulnar M. Shalgumbayeva[1], Zhanna U. Kozykenova[1], Ainur S. Krykpayeva[1], Meruert O. Khamitova[4], Meruyert R. Massabayeva[1]

[1] NJSC "Semey Medical University", Semey, Republic of Kazakhstan;
[2] Nagasaki University, Department of Tumor and Diagnostic Pathology, Nagasaki, Japan;
[3] High Medical School, Faculty of Medicine and Health Care, Al Farabi Kazakh National University, Almaty, Republic of Kazakhstan;
[4] NJSC "Astana Medical University", Nur-Sultan, Republic of Kazakhstan.

Abstract

Relevance. The outbreak of COVID-19 began in late 2019 in Hubei Province, China. Already in the first quarter of 2020, the disease spread around the world. On March 11, 2020, WHO declared a COVID-19 pandemic. The first cases of the disease in Kazakhstan were registered in March 2020.

The aim of the study: a systematic search for scientific information about the socially significant disease COVID-19 and its immunopathogenetic basis for the severity of the course.

Search strategy: Research publications were searched in PubMed, ResearchGate, GoogleScholar databases. A total of 325 literary sources were found, of which 89 were selected for analysis.

Results: To date, clinical experience suggests a wide range of clinical manifestations of COVID-19 from asymptomatic to severe disease with poor survival associated with an aggressive inflammatory response. There is clinical evidence that suggests that cytokine storm is associated with the severity of COVID-19 and is also the leading cause of death. Hyperactivation of the immune system during COVID-19 leads to a sharp increase in the levels of pro-inflammatory cytokines - a cytokine storm that is characterized by systemic inflammation, hyperferritinemia, acute respiratory distress syndrome, systemic inflammatory response syndrome, hemodynamic disturbances, thrombosis, disseminated intravascular coagulation, lung damage and others. organs, multiple organ failure with a poor prognosis.

Conclusion. The cytokine storm caused by SARS-CoV-2 infection is a central mediator of lung damage and, as a result, can cause life-threatening complications. We present several leukocyte and cytokine changes that may help determine the progression and severity of COVID-19 from early to advanced in both mild and severe cases.

Keywords: *COVID-19, cytokine storm, interleukins, SARS-CoV-2, MERS-CoV.*

Резюме

ИММУНОПАТОГЕНЕТИЧЕСКИЕ ОСНОВЫ ТЯЖЕСТИ ТЕЧЕНИЯ COVID-19. ОБЗОР ЛИТЕРАТУРЫ

Асия А. Есенбаева[1]*, Жанна Б. Мусажанова[2,3], Максут С. Казымов[1], Бакытбек А. Апсаликов[1], Дастан Н. Сайдуалиев[1], Гульнар М. Шалгумбаева[1], Жанна У. Козыкенова[1], Айнур С. Крыкпаева[1], Меруерт О. Хамитова[4], Меруерт Р. Масабаева[1]

[1] НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;
[2] Отделение опухолей и диагностической патологии Университета Нагасаки, Нагасаки, Япония;
[3] Высшая школа медицины, факультет медицины и здравоохранения, Казахский национальный университет им. Аль-Фараби, Алматы, Республика Казахстан;
[4] НАО «Медицинский университет Астана», г. Нур-Султан, Республика Казахстан.

Актуальность. Вспышка болезни COVID-19 началась в конце 2019 года, в провинции Хубэй, Китай. Уже в первом квартале 2020 года болезнь распространилась по всему миру. 11 марта 2020 года ВОЗ объявила о пандемии COVID-19. Первые случаи заболевания на территории Казахстана были зарегистрированы в марте 2020 года.

Целью исследования: систематический поиск научной информации о социально значимом заболевании COVID-19 и его иммнопатогенетические основы тяжести течения.

Стратегия поиска: Поиск научных публикаций проводился в базах данных PubMed, ResearchGate, GoogleScholar. Всего было найдено 325 литературных источника, из которых для анализа были отобраны 89.

Результаты: К настоящему времени клинический опыт свидетельствует о широком спектре клинических проявлений COVID-19 от бессимптомной до тяжелой формы заболевания с низкой выживаемостью, связанной с агрессивной воспалительной реакцией. Имеются клинические данные, которые свидетельствует о том, что цитокиновый шторм связан с тяжестью COVID-19, а также является главной причиной смерти. Гиперактивация иммунной системы во время COVID-19 приводит к резкому повышению уровней провоспалительных цитокинов - цитокиновому шторму, который характеризуется системным воспалением, гиперферритинемией, острым респираторным дистресс-синдромом, синдромом системного воспалительного ответа, нарушением гемодинамики, тромбозом, диссеминированным внутрисосудистым свертыванием, повреждением легких и других органов, полиорганной недостаточностью с неблагоприятным прогнозом.

Вывод. Цитокиновый шторм, вызванный инфекцией SARS-CoV-2, является центральным медиатором повреждения легких и, как следствие может вызывать развитие осложнений, угрожающих жизни человека. Мы представляем несколько изменений лейкоцитов и цитокинов, которые могут помочь определить прогрессирование и тяжесть течения COVID-19 от начальной до поздней стадии, как в легких, так и в тяжелых случаях.

Ключевые слова: *COVID-19, цитокиновый шторм, интерлейкины,SARS-CoV-2, MERS-CoV.*

Түйіндеме

КОВИД-19 АУЫРЛЫҚ ДӘРЕЖЕСІНІҢ ИММУНОПАТОГЕНЕТИКАЛЫҚ НЕГІЗДЕРІ. ӘДЕБИ ШОЛУ

Асия А. Есенбаева[1]*, Жанна Б. Мусажанова[2,3], Максут С. Казымов[1], Бакытбек А. Апсаликов[1], Дастан Н. Сайдуалиев[1], Гульнар М. Шалгумбаева[1], Жанна У. Козыкенова[1], Айнур С. Крыкпаева[1], Меруерт О. Хамитова[4], Меруерт Р. Масабаева[1]

[1] «Семей медицина университеті» КеАҚ, Семей қ., Қазақстан Республикасы;
[2] Нагасаки университетінің ісіктер және диагностикалық патология бөлімі, Нагасаки, Жапония;
[3] Медицина жоғарғы мектебі, медицина және денсаулық сақтау факультеті, Әл-Фараби атындағы Қазақ ұлттық университеті, Алматы, Қазақстан Республикасы;
[4] «Астана медицина университеті» КеАҚ, Нур-Султан қ., Қазақстан Республикасы

Кіріспе: COVID-19 індеті 2019 жылдың соңында Қытайдың Хубэй провинциясында басталды. 2020 жылдың бірінші тоқсанында ауру бүкіл әлемге тарады. 2020 жылдың 11 наурызында ДДҰ COVID-19 пандемиясын жариялады. Қазақстанда аурудың бірінші жағдайлары 2020 жылдың наурыз айында тіркелген.

Мақсаты: Әлеуметтік маңызы бар COVID-19 ауруы оның иммунопатогенетикалық негіздерінің ауырлығы туралы ғылыми ақпаратты жүйелі іздеу.

Іздеу стратегиясы: Мақалаларды іріктеу PubMed, ResearchGate, Google Scholar электрондық деректер базасында жүргізілді. Барлығы 325 әдеби дереккөз табылып, оның 89-ы талдауға іріктеліп алынды.

Нәтижесі: Бүгінгі күні COVID-19 клиникалық тәжірибеде клиникалық көріністерінің кең ауқымын көрсетеді, бейсимптомдық формадан ,ауыр ағымына дейін. агрессивті қабыну реакциясына байланысты. COVID-19 ауырлығы цитокиндік дауылмен байланысты екенін және өлімнің басты себебі болуының көрсететін клиникалық дәлелдер бар. COVID-19 ауруы кезінде иммундық жүйенің гиперактивациясы қабынуға қарсы цитокиндер деңгейінің күрт артуына әкеледі – цитокиндік дауыл сипатталады жүйелі қабынумен, гиперферритинемиямен, жедел респираторлық дистресс-синдроммен, жүйелі қабыну реакция синдромымен, гемодинамикалық бұзылулармен, тромбозбен, диссеминирленген тамырішілік коагуляция, өкпенің зақымдануы және т.б. көптеген мүшелердің жеткіліксіздігімен, өмірге қауіп төндіретін болжамы нашар.

Қорытынды: SARS-CoV-2 инфекциясынан туындаған цитокиндік дауыл өкпе жарақатының орталық медиаторы болып табылады және нәтижесінде өмірге қауіп төндіретін асқынуларды тудыруы мүмкін. Біз лейкоциттердің және цитокиндердің бірнеше өзгерістерін ұсынамыз, олар жеңіл және ауыр жағдайларда COVID-19-ның ертеден жоғары деңгейге дейін дамуы мен ауырлығын анықтауға көмектеседі.

Түйінды сөздер: *COVID-19, цитокиндік дауыл, интерлейкиндер, SARS-CoV-2, MERS-CoV.*

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Introduction

In January 2020, the World Health Organization (WHO) declared the spread of the new coronavirus infection COVID-19 as a public health emergency of international concern. In March 2020, according to the WHO, the coronavirus infection COVID-19 acquired the character of a pandemic [89,91], which had not only a medical but also a social impact on the daily lives of people around the world. 19 in a public health field of international concern. To date, as of January 17, 2022, there have been over 330 million confirmed cases and 5,55 million deaths associated with COVID-19 worldwide [74]. In the Republic of Kazakhstan, the incidence of coronovirus infection amounted to 1.16 million, confirmed cases and deaths 18318 [74].

The outbreak of COVID-19 began in Wuhan (Hubei Province), China at the end of December 2019 [77]. Several cases of pneumonia of unknown origin were reported then. The causative agent was identified as a new RNA-containing virus with a β-envelope, which was named severe acute respiratory syndrome coronavirus 2 SARS-CoV-2. SARS-CoV-2 is currently considered the newest member of lineage B of the genus Betacoronavirus (β-CoV) in the family Coronaviridae of the order Nidovirales [92]. Initial comparative genomic analysis showed that SARS-CoV-2 shares almost 79% identity with SARS-CoV and 50% with MERS-CoV [46,90]. According to phylogenetic analysis, SARS-CoV-2 is more similar to SARS-CoV than to MERS-CoV [27].

SARS-CoV and MERS-CoV viruses can rarely cause lower respiratory tract infections, which are more common in newborns, the elderly, and people with comorbidities, while SARS-CoV-2 virus infects the lower respiratory tract in almost all cases, except for those who are asymptomatic. And mild disease. The spectrum of SARS-CoV-2 disease, or COVID-19 by its international name, is wide: from an asymptomatic form of infection to acute respiratory distress syndrome, most often ending in death. SARS-CoV-2 is a recombinant, i.e. a virus in which the genetic the material was partially supplemented with an alien genome of a bat coronavirus and an unknown coronavirus (possibly a snake or pangolin) [90]. Recent data have confirmed that the SARS-CoV virus originated from a mutation in bats, and it has acquired the ability to infect humans. Given the similarity of this virus to bat coronaviruses, it has been suggested that bats could be the main hosts of SARS-CoV-2 [25,92].

Nowadays, data on the pathophysiology of COVID-19 is updating daily. Scientists and doctors from different countries are engaged in the study of a new virus, the study of epidemiology, pathogenesis, and the creation of a vaccine. *Nicastri E. et al.* conducted an epidemiological study of 3711 people infected with COVID-19 on board a cruise ship and found that 17.9% of all infected cases were asymptomatic [50]. Virulence, the human immune response, and complex inflammatory responses play a major role in understanding the host immune response to COVID-19 virus introduction. It has been reported that peripheral immune cells, cytokines, and their receptor expressions play an important role in patients suffering from critical pneumonia in COVID-19 [84]. IL-6 is one of the key cytokines contributing to host defense by stimulating acute phase reactions, hematopoiesis, and immune responses [29]. Serum IL-6 levels have been reported to typically increase during infection, and critical elevations are seen in severe cases [59]. *Chen G. et al.* suggest that SARS-CoV-2 infection may primarily affect T-lymphocytes, leading to a decrease in their number, as well as the production of IFN-γ by CD4 + T cells, these potential immunological markers may be important due to their correlations with disease severity in COVID-19 [10]. There is an increase in serum concentrations of pro- and anti-inflammatory cytokines (IL-2R, IL-6, TNF-α and IL-10) in severe disease, compared with moderate, mild and asymptomatic [84].

Cytokines play an important role in the immune response of the body in response to the persistence of the virus, and cytokine gene polymorphisms affect the overall expression and secretion of cytokines [38]. Single nucleotide polymorphisms can be functional and lead to an increase or decrease in the level of expression of a gene product or its activity. It is believed that the presence of single nucleotide substitutions is one of the factors that determine the individual characteristics of the course and prognosis of the disease. Thus, changes in the genes involved in the body's immune response may contribute to the development and progression of viral diseases.

Purpose of the study. Systematic search for scientific information about the socially significant disease COVID-19 and its immunopathogenetic basis for the severity of the course.

Search strategy. The search for relevant scientific publications was carried out in databases of evidence-based medicine (PubMed, ResearchGate), specialized search engines (GoogleScholar), as well as official WHO

reports and statistical collections. A total of 325 literary sources were found, of which 89 were selected for analysis.

Inclusion criteria: full-text articles published in English and Russian, search depth takes 3 years.

Exclusion criteria: duplication or repetition of information. Publications in the media.

Results and discussion

SARS-CoV, SARS-CoV2, and MERS-CoV infection is accompanied by fever, dry cough, dyspnoea, myalgia, weakness, leukopenic tendency, and signs of progressive pneumonia, which can later cause acute respiratory distress syndrome (ARDS). The symptoms of the SARS-CoV2 virus seem to be milder than SARS or MERS infection, but eventually mortality exceeds and the disease becomes deadly [13]. This suggests that their pathogenesis may also be similar [27]. Pathogenetically, SARS-CoV2 is characterized by viremia, local and systemic immunoinflammatory process, hyperactivity of the coagulation cascade, endotheliopathy, hypoxia, which leads to the development of micro- and macrothrombosis; proceeds from asymptomatic to clinically pronounced forms with intoxication, fever, damage to the endothelium of blood vessels, lungs, heart, kidneys, gastrointestinal tract, central and peripheral nervous systems with the risk of developing severe complications. The main target of SARS-CoV-2 is the lungs. In pathogenesis, two main mechanisms can be distinguished that mutually aggravate each other and can lead to the development of ARDS - this is direct viral damage to alveocytes with the development of an immunoinflammatory syndrome and the development of micro- and macrothrombosis of the pulmonary vessels and obstructive thromboinflammatory syndrome [59].

The main mechanism of transmission of coronavirus infection is airborne (or airborne dust), in which pathogens are localized in the mucous membrane of the respiratory tract and transferred to a new organism through the air. In this way of transmission, the pathogen enters the external environment when sneezing and coughing with drops of liquid and is introduced into the human body by inhalation of air containing infected particles. If the particles are small, they are in the air for some time in the form of an aerosol (droplets suspended in the air), and if the particles are larger, they settle on various surfaces at a distance of up to two meters around the sick person [54]. After entering the respiratory tract, the main targets of the virus are respiratory tract epithelial cells, alveolar epithelial cells and vascular endothelial cells [3]. To date, Kazakhstan has adopted a classification according to the protocol for diagnosing and treating COVID-19 according to the severity of the course: mild severity - without lung damage; moderate-COVID-19 associated pneumonia affecting 25-50% of the lungs (CT-2); severe course -COVID-19 associated pneumonia with >75% lung involvement (CT-4); severe course - COVID-19 associated pneumonia with 50-75% lung involvement (CT-3) and extrapulmonary manifestations, as well as the presence of complications and concomitant diseases; extremely severe or critical severity - bilateral subtotal pneumonia (ARN, ARDS, shock, MODS) [17].

The coronavirus genome encodes four major proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). The S protein is the most immunogenic part of coronaviruses, it binds to angiotensin-converting enzyme-2 (ACE-2) receptors for insertion into the host cell [40]. About 75% of the SARS-CoV2 genome is similar to the SARS-CoV genome. The virus entering the cell binds the peplomer protein to the ACE-2 receptor, then releases the RNA genome in the cytoplasm of the cell and replicates, which leads to the formation of new viral particles and its spread along the communicating airways. At this stage, the infection is asymptomatic, but the person is contagious and the virus can be detected by PCR [30]. The infection then spreads to the rest of the upper respiratory tract, resulting in symptoms of fever, malaise, and dry cough. During this period, infected cells release the chemokine ligand CXCL10, interferons beta and gamma, and the immune response may be sufficient to prevent further spread of infection, which occurs in most cases. In about a fifth of those who become ill, the infection spreads to the lower respiratory tract with the development of more severe symptoms [2]. When the virus affects the alveoli, a local inflammatory reaction occurs with the release of a large number of cytokines and chemokines by immune effector cells. In patients infected with SARS-CoV2, high levels of pro-inflammatory cytokines and chemokines were found in the blood, including: IL1-β, IL1RA, IL7, IL8, IL9, IL10 and others [57]. Increased levels of pro-inflammatory cytokines are associated with the severity of lung damage (increased ground glass effect). In some patients, this activation becomes so massive that a cytokine storm develops. The ensuing cytokine storm triggers a strong inflammatory immune response that contributes to the development of ARDS, a fatal multiple organ failure. In severe cases of SARS-CoV-2 infection, similar to SARS-CoV and MERS-CoV infections [30,47]. Patients infected with COVID-19 showed higher white blood cell counts and increased levels of pro-inflammatory cytokines [27]. The direct cause of death from COVID-19 is the complications of the cytokine storm, damage to the lungs and other organs: the heart, kidneys and liver [48,58,67,69].

ZhangWetal found that in patients with severe COVID 19 disease, a decrease in the level of T-lymphocytes, including CD4 and CD8 subtypes and especially NK cells in the blood [85]. The number of regulatory T cells is also very low. An early sign of the disease is severe lymphopenia, which precedes the clinical manifestations of pneumonia and tends to normalize as the patient's condition improves. In many countries, one of the diagnostic criteria for the severity of the disease is lymphopenia. Even with low levels of CD4- and CD8-T-lymphocytes express a high amount of HLADR4 and CD38, thereby they show hyperactivity. In severe cases of the disease, the total number of leukocytes and neutrophils, as well as the neutrophil/lymphocyte ratio (NLR), increases. In patients with COVID-19 infection, NLR can be used as a follow-up parameter [41,81]. CD8 T-lymphocyte levels are restored after 2-3 months, recovery of CD4 T-lymphocytes during SARS-CoV infection can take almost a year [44,62,83,85]. The results of the autopsy showed that in addition to the low number of lymphocytes in the blood, there is also atrophy of secondary lymphoid organs, including the lymph nodes and spleen. Immunohistochemical staining revealed a decrease in the number of CD4-positive and CD8-positive T cells in the lymph nodes and spleen [79,80]. In the other half of patients, on the contrary, the number of monocytes and

macrophages increases, which leads to an increase in the level of pro-inflammatory cytokines, such as interleukin IL-6, IL-1, tumor necrosis factor (TNF) α and IL-8, which contribute to the emergence of a cytokine storm in patients . A persistent increase in D-dimer levels worsens the prognosis in patients with COVID-19. The development of DIC is another problem characterized by prolonged prothrombin time and activated partial thromboplastin time, high levels of fibrin degradation products, and severe thrombocytopenia, which can be life-threatening [86].

High levels of inflammatory mediators and immunoglobulins can lead to increased blood viscosity; mechanical ventilation and central venous catheterization may additionally cause damage to the vascular endothelium in severely or critically ill patients. Anticardiolipin antibody levels were also high in the small groups. Thus, in people infected with COVID-19, the combination of all of the above factors can lead to deep vein thrombosis or even fatal pulmonary thromboembolism [86,87]. COVID-19 infection is accompanied by an aggressive inflammatory response with the release of large amounts of pro-inflammatory cytokines known as a “cytokine storm [21].” The release of cytokines in response to infection can lead to mild or severe clinical manifestations [30].

In the case of SARS, infected hematopoietic cells, macrophage monocytes, and other immune cells induce increased secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-α/-γ with reduced levels of anti-inflammatory cytokines [5,15,75]. Similarly, MERS-COV infection results in delayed but increased production of IFN-α and pro-inflammatory cytokines like IL-6, IL-8 and IL-1 [37,66,89]. Such elevated levels of cytokines have been associated with multiorgan dysfunctional syndrome (MODS) and ARDS due to the accumulation of multiple immune cells such as macrophages, neutrophils, and dendritic cells in the lungs, causing alveolar damage and edema [24,34,49,66]. Similarly, in patients with COVID-19, the secretion of cytokines and chemokines that attract immune cells to the lungs has been increased, causing ARDS, which is fatal for the critically ill [20,66,88]. Signature cytokines in critically ill COVID-19 patients were consistent with those in SARS and MERS patients, i.e. increased expression of IL-6, TNF-α, macrophage inflammatory protein 1-α (MIP-1α), MCP3, GM-CSF, IL- 2, and IP-10 along with elevated chemokines (IP-10, CCL2/MCP1, CXCL1, CXCL5) have also been detected in SARS-CoV coronavirus-2 infection [18,48,66,73,91]. In children, elevated inflammatory markers include IL-6, IL-1, and C-reactive protein along with serum procalcitonin [64,66]. In a case study, a 14-year-old child with a cytokine storm was treated with anakinra (an IL-1 receptor antagonist) to stabilize respiratory disease and other clinical symptoms [39,51]. Transcriptome analysis of PBMC and BALF showed that a number of immune regulators were activated, especially CXCL10, in relation to BALF. This study also reported that several apoptotic genes and P53 signaling molecules were upregulated, indicating a possible cause of lymphopenia in these patients [66,78].

Cytokines are produced by several immune cells, including innate macrophages, dendritic cells, natural killer cells, and adaptive T and B lymphocytes. The three most important pro-inflammatory cytokines of the innate immune response are IL-1, TNF-α, and IL-6 [21]. Tissue macrophages, mast cells, endothelial and epithelial cells are the main source of these cytokines. The "cytokine storm" is the result of a sudden surge in pro-inflammatory cytokines, including IL-6, IL-1, TNF-α, and interferon [21]. An increase in cytokines leads to an influx of various immune cells, such as macrophages, neutrophils and T cells, from the circulation to the site of infection with a devastating effect on human tissues as a result of destabilization of endothelial cellular interactions with cells, damage to the vascular barrier, damage to capillaries, diffuse alveolar damage, multiple organ failure and ultimately death [21,30]. Lung injury is one of the consequences of the cytokine storm, which can progress to acute lung injury or its more severe form ARDS [21,60]. Although the exact mechanism of ARDS in patients with COVID-19 is not fully understood, excessive production of pro-inflammatory cytokines is thought to be one of the major contributing factors [12,21,27,30,36]. Plasma cytokine levels in 41 confirmed cases of COVID-19 in China revealed elevated levels of IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α and VEGF in patients admitted to the intensive care unit, as well as patients not requiring resuscitation, compared with healthy individuals [21]. All patients included in this study had pneumonia and 1/3 of the patients were admitted to the intensive care unit, and six of these patients died [21,27]. A multicenter retrospective study of 150 COVID-19 patients in China assessed predictors of mortality from COVID-19 [21,58]. The study analyzed data from 82 cases that resolved from COVID-19 and 68 cases that died from COVID-19 and reported significantly higher levels of IL-6 in deaths than in cases that resolved [21,58]. Another study analyzing data from 21 patients in China reported elevated levels of IL-10, IL-6 and TNF-α in severe cases (n=11 patients) compared to moderate cases (n=10 patients) [10,21]. A similar study by Gao et al. evaluated 43 patients in China and reported that IL-6 levels were significantly higher in severe cases (n=15) than in mild cases (n=28) [21,24]. Also, Chenetal. studied a total of 29 patients with COVID-19 divided into three groups according to relevant diagnostic criteria and found that IL-6 was higher in critical cases (n=5 patients) than in severe cases (n=9 patients), and that IL-6 was higher in severe cases than in mild cases (n=15 cases) [11,21].

In a study on IL-6 and TNF, Yangetal studied 48 cytokines in patients with COVID-19, 14 of which were markedly increased [30,87]. Among these 14 cytokines, IP-10, MCP-3 and IL-1ra have been identified as biomarkers of disease severity and mortality [30]. They also found that IP-10 levels were markedly higher in patients with severe disease compared to those with mild disease [30,32]. A report of 10 severely ill COVID-19 patients showed a marked increase in CCL5 (CC chemocin ligand 5, RANTES); It is important to note that treatment with CCR5-blocking antibody led to a decrease in the level of IL-6 in the blood, a decrease in the expression of genes associated with IFN, a decrease in the SARS-CoV-2 viral load, and the restoration of immune homeostasis [30,53]. *Liu et al.* [45] reported that 38 cytokines from COVID-19 patients were significantly increased and 15 cytokines (IL-12, IL-1ra, IP-10, PDGF-BB [platelet growth factor-BB], TNF, IFN-γ, M-CSF [macrophage CSF], IL-17, HGF, G-CSF, IL-2, IL-4, IL-

10, IL-1α and IL-7) were associated with disease severity. In addition, some inflammatory markers such as CRP and D-dimer were also markedly elevated [28,30]. However, in contrast to the results in patients with SARS, patients with COVID-19 showed an increase in anti-inflammatory cytokines such as IL-10 and IL-4 [30,72], suggesting an increased Th2 response and subsequent pulmonary interstitial fibrosis. Finally, single-cell RNA sequencing results from early recovering patients infected with SARS-CoV-2 indicated that IL-1β and M-CSF may be novel mediators in the cytokine storm-associated inflammatory response [30,68,72]. SARS and MERS patients also experienced a Th17-type cytokine storm caused by the mobilization of Th17 responses [22,30,31]. It has been reported that a large number of CCR4 CCR6 Th17 cells, which are at least partially attributed to this immunopathology, were also present in a COVID-19 patient with ARDS [30,76] markedly elevated cytokines (i.e., IL-1, IL-17, TNF, and GM -CSF) in COVID-19 patients have been associated with Th17 responses [22,30,31,45]. These data suggest that a Th17-type cytokine storm may lead to or be associated with the onset of organ damage commonly seen in patients with severe COVID-19 [30,77].

High levels of IL-6 may also contribute to an increase in neutrophil cells and a decrease in lymphocytes. Clearly, IL-6 may influence the development of ARDS in patients with COVID-19 [30,87], and an increase in IL-6 may be a useful marker for the onset of severe disease. Furthermore, since mildly centric coagulopathy may also play an important role in the pathophysiology of severe COVID-19 patients [23,30], IL-6 may contribute to this pathology by inducing coagulation cascades [30,33]. However, hypercoagulability, together with high levels of D-dimers, fibrinogen, and CRP, in patients with COVID-19 differs from the disseminated intravascular coagulation described in more severe inflammatory conditions [30,52,66]. In addition, IL-6 levels may vary in patients with COVID-19 in relation to disease severity [28,30,83].

The trigger for a cytokine storm is an uncontrolled immune response leading to the continuous activation and expansion of immune cells, lymphocytes and macrophages that produce a huge amount of cytokines, resulting in a cytokine storm [30]. The clinical outcomes of CS are associated with the action of pro-inflammatory cytokines such as IL-1, IL-6, IL-18, IFN-γ, and TNF-α [60].

Release of cytokines by natural killer (NK) cells and macrophages, along with activated T cells and humoral responses, may help eliminate infection accompanied by effector mechanisms such as antibody-dependent cellular-mediated cytotoxicity (ADCC) [4,30]. These reactions are triggered to keep the pathogen under control. For example, local cytokines such as IFN-α/β and IL-1β produced by epithelial cells can protect nearby cells by stimulating IFN-stimulated gene expression while simultaneously activating immunocompetent cells such as NK cells [30]. This increases the lytic potential of the NK cell and fuels the secretion of IFN-γ [9,30]. In addition to NK cells, once myeloid cells, such as resident macrophages, are activated by IFN-γ, this enhances subsequent TLR-mediated stimulation. This includes the release of high levels of TNF, IL-12 and IL-6, which in turn can further modulate NK cells [8,30]. Although IL-12 acts to increase NK IFN-γ secretion, high levels of IL-6 may also limit the immune response by its effect on NK cell cytotoxic activity by reducing intracellular perforin and granzyme levels [16,19,30].

As the disease progresses, T cell and antibody responses generate additional cytokine responses, resulting in more or sustained antigen release and added TLR ligands due to viral cytotoxicity [30,42]. Once these responses are triggered, host or pathogen related factors (such as decreased viral load, anti-inflammatory responses, etc.) kick in to prevent an unregulated response or CRS if the pathogen or host related responses are not sufficient to suppress the production of pro-inflammatory cytokines. , then tissue damage can occur and go into multiple organ failure [30]. For example, the absence of a negative feedback mechanism in IL-10 and IL-4 is expected to increase the severity of cytokine responses to pathogenic CRS or cytokine storm [30,63].

The relative frequencies of circulating activated CD4+ and CD8+ T cells and plasmablasts are increased in Covid-19 [47]. In addition to elevated levels of systemic cytokines and activated immune cells, some clinical and laboratory changes are also observed in Covid-19, such as elevated levels of CRP and d-dimer, hypoalbuminemia, renal dysfunction, as in cytokine storm disorders. It has been found that laboratory test results reflecting hyperinflammation and tissue damage suggest worse outcomes with Covid-19 [6]. Cytokine storm is one of the common causes of death during the recently declared COVID-19 pandemic. SARS-CoV-2 infection-induced cytokine storm is generally thought to be a central mediator of lung injury and, as a result, ARDS found in patients with COVID-19 in severe or critical illness [30]. We present several leukocyte and cytokine changes that can help determine the progression of COVID-19 from early to advanced in both mild and severe cases [30].

In public health, population vaccination is the most important measure to protect people from COVID-19 because SARS-CoV-2 is a highly contagious virus [1]. In the first 9 months since the emergence of the virus, preclinical development of more than 200 vaccines began, 36 of which entered clinical trials [65]. On March 13, 2020, the first doses of the vaccine were tested in humans. By September 24, 2020, the SARS-CoV-2 vaccination landscape included 43 clinical trial candidates and more than 200 candidates [65]. The main problem in the development of a vaccine against SARS-CoV-2 is the likelihood of a rapid disappearance of antibodies. Previously, it was found that CoV infection is unable to induce a long-lived antibody response, leading to re-infection of people with the same virus after a long period, although this phenomenon is not widespread [65]. Another challenge associated with the development of a vaccine against SARS-CoV-2 is to ensure the prevention of disease exacerbations. A vaccinated person may develop a more severe condition with COVID-19 than an unvaccinated person. This phenomenon is supported by a study on an experimental SARS vaccine in which vaccinated ferrets developed critical liver inflammation in response to a viral infection [70]. A significant challenge in COVID-19 vaccine development is the frequent mutations in the SSARS-CoV-2 protein, the most common target antigen in current efforts, limiting the effectiveness of first-generation COVID-19

vaccines and even requiring recovered patients to be vaccinated against the mutated virus [35,71,81]. Therefore, an ideal COVID-19 vaccine platform should allow easy and rapid deployment of newly mutated and identified antigens. Current preclinical and clinical studies of COVID-19 vaccines primarily aim to generate neutralizing antibodies against SARS-CoV-2 and desirably induce the production of memory T and B cells [14,55,94]. Effective and long-term protection against SARS-CoV-2 infection requires well-organized innate, humoral, and cellular immunity.

Thus, COVID-19 has affected both the healthcare system and other economic, sociocultural systems. The COVID-19 pandemic may end, but the consequences will remain and continue to create serious problems. COVID-19 starts as a simple viral infection, but after a while it gets out of control and progresses to death with the development of a cytokine storm and serious damage organs.

Conclusion. We hypothesize that it is likely that a certain percentage of people have genetic predisposing factors that contribute to the development of the cytokine storm that leads to severe COVID-19. The search for genetic markers for the possibility of taking timely preventive measures to prevent severe and extremely severe course of the coronavirus infection is a priority strategy of modern medicine.

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***Coresponding Author:**
Yessenbayeva Assiya - Department of Family Medicine, NCJSC «Semey Medical University», Semey, Republic of Kazakhstan
Mailing address: Republic of Kazakhstan, 071400, Semey, Abaya st., 103.
e-mail: erasyl.majdan@mail.ru
Mob.: 87772361697