Complex Analysis of New Unique Human Society Life in COVID-19 Pandemic in Eight Coordinate System

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The World lives in eight coordinates and it would have been surprising even to Newton.

Abstract: The article presents deep and complex analysis based on the changes of life of human society during the COVID-19 pandemic. The World as never before has a global common enemy and everyone is in danger, no matter where he lives and what is the occupation. The life new dimensions are considered as an 8-coordinate system where the new 4 coordinates – coronavirus, "virus" of poverty, "virus" of chronically ill people and scientists as a new leading factor of the world. Therefore, a simple solution for prevention and regulation of pandemic doesn't exist. Countries and outbreaks are represented by 4 everlasting coordinates – three for space and one for time measurement. Life of human society is conditionally divided of 4 hierarchic levels. Interactions between them have to be studied by scientists from all areas in order to win this world challenge where all humans are on the same side of the barricade. The presented analysis could be extremely useful for explaining the errors made by leaders and to show them that the new reality requires relevant and effective decisions based on scientific complex analyzes and taking into account the four hierarchic levels of knowledge.

Keywords: COVID-19, System Analysis, Eight coordinate system, Human life, Coronavirus, Poverty, Chronically ill people.

Introduction

Human society faced something unique as a danger in November 2019. It was a new virus SARS-CoV-2 which attacks the human being in a non-precedential way. The worldwide spread of SARS-CoV-2 began afterwards favored by the dynamic international transport and global communication in business, economy, tourism, science exchange programs, etc. After twelve months more than 65 million people have been infected and currently more than 1.4 million people (December 04, 2020) died worldwide. The chaos and fear in every country increased because of the lack of knowledge in the procedure of making decisions in all main sub-systems of human society, namely, healthcare, economy, business, transport and behavior in the working places and daily life. The many unknowns in virology to epidemiology aspects about this new pathogen (mechanism of spread, reservoirs, transfer, survivability in the environment, pathogenesis and pathological effects on human health, etc.) required to apply the out of date old but the only possible trial and error method and principles of analogy in medical protocols. Unfortunately, the price of every political error to control and preserve the society during this period was paid with human lives.

Here, we are not going to discuss the emotional and psychological impact of any errors on humans and their response about the restriction measures made by political leaders of particular countries.

The scientific and research efforts to understand the biology of SARS-CoV-2 and control the virus dissemination (COVID-19) and vulnerability of the human beings are the milestones of every success of the overall system (i.e., the human society behavior).

Hence, when analyzing the new behavior of human society during this period, we are going to try to build the architecture of new human system which already includes 8 coordinates (see Fig. 1). Our capacity for applying system analysis have been serving us more than 30 years to describe, study, optimize and design many biochemical reactors [20, 21, 25, 26], biotechnological

[27, 30], and chemical systems [38, 52], wastewater treatment processes [23, 38, 48] and photobioreactors [14, 24, 28, 29, 31, 43].

First, it is imperative and necessary to clarify what life is like in the new reality with COVID-19 pandemic. Since November 2019, the world lives in a new 8-coordinate system (Fig. 1).

A) The eternal four coordinates:

- three for space (x, y, z);
- one for *time* (t).

B) The new four coordinates, are:

- the fifth is the SARS-CoV-2 virus;
- the sixth is the *Poverty "virus"* (COVID-19's twin brother);
- the seventh is a "virus" of the Chronically Ill People;
- the eighth coordinate are the Scientists and all people on the front line: doctors, medical staff, people working in pharmacies, grocery stores, transport workers, police, military, etc.



Time coordinate (t): $2020 \rightarrow$

Fig. 1 Life in COVID-19 – new 8 coordinate system. Analysis of hierarchic levels and sub-systems. Note: Covid-19 virus (v_c) in first hierarchic level (HL I) means that this diseases is provoked by SARS-CoV-2.

The behavior of this 8-coordinate system is not known so far and cannot be described and formalized because the main sub-system in the first hierarchic level is unknown (Fig. 1).

Mathematical equation which can be written in this moment is as follows:

$$LHSC_{19} = f(x, y, z, t, v_c, v_p(v_c), v_{cd}(v_c), Sc),$$
(1)

where $LHSC_{19}$ – is life of human society during COVID-19 pandemic; x, y, z – stand for the space coordinates determining location of every country, as well as the internal position of critical places (e.g. cities and/or regions); t – is the time in which humans live from November, 2019 up to now; v_c – is SARS-CoV-2 virus coordinate; v_p – is virus of poverty, which is a function of v_c ; v_{cd} – is virus of chronic disease, which is a function of v_c , as well; Sc – stands for the scientists of all areas as a new crucial coordinate. Only they are able to solve the above equation by formalizing and combining the knowledge from every sub-system. It will contribute to building a complex but robust model of the society to be used for making decisions by the government and/or other decision making authorities.

First hierarchic level (HL I):

Causes - SARS-CoV-2/COVID-19, poverty and chronic diseases

Understanding, mathematical and logical formalization of SARS-CoV-2/COVID-19 virus sub-system and how it is directly connected to its other sub-systems and their relationships is a

milestone of overall success in right interpretation, analysis, and prediction of changes in human life and society.

First, the SARS-CoV-2is a new pathogen with unknown characteristics of infection and action of damage on human organs, behavior and mentality. This reflected in shock and desperation in society because at the beginning humans were losing life without having the answer how to stop it.

The danger we faced is COVID-19 - a new disease caused by a new strain of coronavirus (SARS-CoV-2) that has not been previously identified in humans and animals despite that coronavirus infections are zoonoses in their origin and evolution.

Together with the high population density of humans and the wide range of host animals (domestic animals, snakes, bats, civets, camels, etc.) being in contact with man and thus creating conditions the virus to jump the species boundary is in confirmation of the hypothesis of its natural origin. Comparative analysis of SARS-CoV-2 genomic data (if not being proved otherwise through a deeper and more comprehensive analysis) clearly shows that this virus is not a laboratory construct or a purposefully manipulated virus. SARS-CoV-2 is the seventh coronavirus known to infect humans. SARS-CoV, MERS-CoV (Middle East respiratory syndrome coronavirus) and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43 and 229E are associated with mild symptoms [1]. Human coronaviruses such as 229E and NL63 are responsible for common cold and croup and belong to α coronaviruses. In contrast, SARS-CoV, MERS-CoV and SARS-CoV-2 are classified to β coronaviruses [42].

HLI-Sub-system 1: Understanding of pathogenesis of COVID-19 in the human body

The scientific literature abounds with data on SARS-CoV-2 but two notable genomic features have been identified:

1. Mutations in the receptor-binding domain of SARS-CoV-2

On the basis of structural studies [49, 50, 53] and biochemical experiments [32, 53, 60], SARS-CoV-2 seems to have a receptor-binding domain (RBD) that binds with high affinity to Angiotensin-converting enzyme 2 (ACE2) from humans, ferrets, cats and other species with high receptor homology [50]. While the analyses above suggest that SARS-CoV-2 may bind human ACE2 with high affinity, computational analyses predicts that the interaction is not ideal and that the RBD sequence optimal for receptor binding is different from those shown in SARS-CoV [44, 50]. Thus, the high-affinity binding of the SARS-CoV-2 spike protein to human ACE2 is most likely the result of natural selection on a human or human-like ACE2 that permits another optimal binding solution to arise.

2. SARS-CoV-2 polybasic cleavage site (RRAR)

The second notable feature of SARS-CoV-2 is a polybasic cleavage site (RRAR) at the junction of S_1 and S_2 , the two subunits of the spike [49]. This allows an effective cleavage by furin and other proteases and has a key role in determining viral infectivity and host range [39]. In addition, a leading proline is also inserted at this site in SARS-CoV-2; thus, the inserted sequence is PRRA. The functional consequence of the polybasic cleavage site in SARS-CoV-2 is unknown, and it will be important to determine its impact on transmissibility and pathogenesis in animal models. Experiments with SARS-CoV have shown that insertion of a furin cleavage site at the S_1 - S_2 junction enhances cell-cell fusion without affecting viral entry [10]. The function of the predicted O-linked glycans is unclear, but they could create a 'mucin-like domain' that shields epitopes or key residues on the SARS-CoV-2 spike protein [2].

Several viruses utilize mucin-like domains as glycan shields involved in immunoevasion [2]. Although prediction of O-linked glycosylation is robust, further experimental studies are needed as soon as possible to determine if these sites are used in SARS-CoV-2.

HLI-Sub-system 2: Understanding of infection and spread of COVID-19

1. Virus life cycle

The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion (penetration), and release their contents inside the host cells. Viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released.

2. Virus structure

Coronaviruses consist of four structural proteins; spike (S), membrane (M), envelop (E) and nucleocapsid (N) [5]. The spike is composed of a transmembrane trimetric glycoprotein protruding from the viral surface, which determines the diversity of coronaviruses and host tropism. It comprises two functional subunits; S1 subunit is responsible for binding to the host cell receptor and S₂ subunit is for the fusion of the viral and cellular membranes. ACE2 was identified as a functional receptor for SARS-CoV [33]. Structural and functional analysis showed that the spike for SARS-CoV-2 also bound to ACE2 [7, 32, 49]. ACE2 expression is high in lung, heart, ileum, kidney and bladder [62]. In lung, ACE2 is highly expressed on lung epithelial cells. Whether or not SARS-CoV-2 binds to an additional target needs further investigation. Following the binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage. A two-step sequential protease cleavage to activate spike protein of SARS-CoV and MERS-CoV was proposed as a model, consisting of cleavage at the S₁/S₂ cleavage site for priming and a cleavage for activation at the S₂ site, a position adjacent to a fusion peptide within the S₂ subunit [3, 37, 40]. After the cleavage at the S₁/S₂ cleavage site, S₁ and S₂ subunits remain non-covalently bound and the distal S₁ subunit contributes to the stabilization of the membrane-anchored S₂ subunit at the prefusion state [49]. Subsequent cleavage at the S₂ site presumably activates the spike for membrane fusion via irreversible, conformational changes. The coronavirus spike is unusual among viruses because a range of different proteases can cleave and activate it [4]. The unique characteristics of SARS-CoV-2 among the coronaviruses is the existence of furin cleavage site ("RPPA" sequence) at the S1/S2 site. The S₁/S₂ site of SARS-CoV-2 in a study was entirely subjected to cleavage during biosynthesis in a drastic contrast to SARS-CoV spike, which was incorporated into assembly without cleavage [49]. Although the S_1/S_2 site was also subjected to cleavage by other proteases such as transmembrane protease serine 2 (TMPRSS2) and cathepsin L [15, 40], the ubiquitous expression of furin likely makes this virus extremely pathogenic.

3. Host response to SARS-CoV-2

Because ACE2 is highly expressed on the apical side of lung epithelial cells in the alveolar space, this virus can likely enter and destroy them [13, 19]. This matches with the fact that the early lung injury is often seen in the distal airway. Epithelial cells, alveolar macrophages and dendritic cells (DCs) are three main components for innate immunity in the airway [56]. DCs reside underneath the epithelium. Macrophages are located at the apical side of the epithelium. DCs and macrophages serve as innate immune cells to fight against viruses till adaptive immunity is involved.

T cell-mediated responses against coronaviruses have been previously reviewed [6]. T cell responses are initiated by antigen presentation via DCs and macrophages. How does SARS-CoV-2 enter antigen-presenting cells (APCs)? DCs and macrophages can phagocytize apoptotic cells infected by virus [11]. For example, virus-infected apoptotic epithelial cells can be phagocytized by DCs and macrophages, which lead to antigen presentation to T cells. Or DCs and macrophages may be infected with virus primarily? Based on the Immunological Genome Database (http://rstats.immgen.org), the expression of ACE2 on (splenic) dendritic cells and alveolar macrophages is present but limited. Determining whether or not SARS-CoV-2 uses another protein to bind to APCs helps to answer this question. SARS-CoV can also bind to dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein (DC-SIGNR, L-SIGN) in addition to ACE2 [18, 36, 55]. DC-SIGN is highly expressed on dendritic cells and macrophages. Another target for SARS-CoV-2, if any, can help the virus to directly infect DCs and alveolar macrophages. This needs future research. These APCs move to the draining lymph nodes to present viral antigens to T cells. CD4⁺ and CD8⁺T cells play a critical role. CD4⁺T cells activate B cells to promote the production of virus-specific antibody, while CD8⁺T cells can kill viral infected cells.

HL I – Sub-system 3: Understanding of the effects of SARS-CoV-2 in human risk group

Various immunological studies comprising COVID-19 patients were reported. Patients with a severe disease showed lymphopenia, particularly the reduction in peripheral blood T cells [41, 61]. These patients were reported to have increased plasma concentrations of proinflammatory cytokines, including interleukin 6 (IL-6), IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1α (MIP1 α), and tumor necrosis factor α (TNF- α) [16, 41, 61]. The more severe conditions patients were in, the higher their IL-6 levels were. CD4⁺and CD8⁺T cells were activated in those patients as suggested by higher expression of CD69, CD38 and CD44. Higher percentage of checkpoint receptor Tm3⁺PD-1⁺ subsets in CD4⁺ and CD8⁺T cells showed that T cells were also exhausted. NK group 2 member A (NKG2A), another marker for exhaustion was elevated on CD8+ T cells [59]. Exhaustion of T cells could have led to the progression of the disease. Another interesting finding was that aberrant pathogenic CD4⁺T cells with co-expressing interferon γ (IFN- γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were seen in COVID-19 patients with a severe disease [61]. GM-CSF production from T cells has been previously reported as a response to virus infection. GM-CSF can augment T cell function and help in the differentiation of innate immune cells, but it can initiate tissue damage at excess [8, 17]. It is worth mentioning that these immunological studies were exclusively reported from adult patients. Immunological responses in pediatric population needs to be examined.

The study of SARS-CoV showed that virus infected lung epithelial cells produce IL-8 in addition to IL-6 [56]. IL-8 is a well-known chemoattractant for neutrophils and T cells. Infiltration of a large number of inflammatory cells was observed in the lungs from severe COVID-19 patients [47, 54], and these cells presumably consist of a constellation of innate immune cells and adaptive immune cells. Among the innate immune cells, it is expected the majority to be neutrophils. Neutrophils can act as double-edged sword as neutrophils can induce lung injury [22, 34, 57]. The majority of the innate immune cells are expected to be neutrophils. Neutrophils can act as they can induce lung injury [22, 34, 57]. The majority of the observed infiltrating adaptive immune cells were likely T cells, considering that the significant reduction in circulating T cells was reported. CD8⁺T cells are the primary primary cytotoxic T cells. Severely sick patients also showed pathological cytotoxic T cells

derived from CD4⁺ T cells [9]. These cytotoxic T cells can kill virus but also contribute to lung injury [46]. Circulating monocytes respond to GM-CSF released by these pathological T cells. CD14⁺CD16⁺ inflammatory monocyte subsets, which seldom exist in healthy controls, were also found at a significantly higher percentage in COVID-19 patients. These inflammatory CD14⁺CD16⁺ monocytes had high expression of IL-6, which likely accelerates the progression of systemic inflammatory response.

An interesting finding is that ACE2 is significantly expressed on innate lymphoid cells (ILC) – ILC2 and ILC3. NK cells are a member of ILC1, which constitute a large portion of ILCs in the lung (~95%). ILC2 and ILC3 work for mucous homeostasis. So far there is a very limited study of ILC2 and ILC3 in coronavirus infection.

In addition to respiratory symptoms, thrombosis and pulmonary embolism have been observed in severe diseased patients. This is in line with the finding that elevated d-dimer and fibrinogen levels were observed in those patients. The function of the endothelium includes promotion of vasodilation, fibrinolysis, and anti-aggregation. Because endothelium plays a significant role in thrombotic regulation [51], hypercoagulable profiles seen in severe diseases likely indicate significant endothelial injury. Endothelial cells also express ACE2 [35, 45]. Of note, the endothelial cells represent one third of lung cells and microvascular permeability as a result of the endothelial injury can facilitate viral invasion [58].

In conclusion, the SARS-CoV-2 is easily transmittable between humans and has caused a pandemic worldwide. The number of death tolls continues to rise and a large number of countries have been forced to implement social distancing and lockdown. Lack of targeted therapy continues to be a problem. Epidemiological studies showed that elder patients are more susceptible to severe diseases, while children tend to have milder symptoms. Also, the number of male patients is higher – the data suggested that more men than women suffered from severe disease and died.

The mean incubation period is 5.2 days. In the multivariable analysis, the presence of coronary artery disease, diabetes and hypertension was also considered to be risk factors. The combined case-fatality rate is 2.3%. It must be noticed that full decoding of SARS-CoV-2 genome sequencing will tremendously help to accelerate production of vaccine and drugs against it.

On the base of above data, the analysis of HL I shows undoubtedly that the study and formalization of this level is crucial in life saving. Further studies on virus biology, transmission of infection, virulence factors and pathogenetic mechanisms, immune response will throw light and correct the direction whether earlier implementation of interventions from decision makers such as social distancing, population behavioral change, and contact tracing would have been able in full power to confront and hold back the epidemic and further will correct the direction. The overall control of the 8-coordinate system is based exclusively on the progress in understanding of the HL I in order for human society to succeed in making a vaccine and drugs as soon as possible for the well-being of humans not ONLY in one particular country, but on the whole planet.

Once again, SARS-CoV-2 virus (and COVID-19 disease) sub-system established new influential and interconnected coordinates, namely, poverty "virus" (v_p) and "virus" of chronic disease (v_{cd}) and scientists (*Sc*) as an informal leader of the World. The above analysis raises the question of how fast this sub-system can be understood and how fast further human action will reach the target to create a new vaccine and effective drugs against the virus. Society

urgently needs this knowledge, because poverty is a more devastating and harrowing virus which will destroy poor countries and economics. On the other hand, risk groups (v_{cd}) cannot remain under quarantine for a prolonged time (relatively 2-3 months) because their health will be damaged irrevocably. Any knowledge about SARS-CoV-2 virus (and COVID-19 disease) sub-system which can be described by mathematical models, instantly will reflect to the better prediction in all areas. It means experimental data *in vitro* and *in vivo* from scientific experiments in virology, infectious microbiology, immunology, biochemistry and molecular biology must be available for mathematicians and statisticians in order to create phenomenological and reliable practical models.

Second hierarchic level (HL II):

Economy aspects and epidemiological control strategies and policies

HL II directly connects and depends on all obtained knowledge from the first level. Quarantine policy of COVID-19 pandemic, social distance and human isolation is determined exclusively from our knowledge about virus features to infect humans and its spread into population. Nevertheless, all measures in quarantine are connected and depend on the third hierarchic level (HL III) where financial power and resources of a particular country can be taken into account. The leaders and decision makers are dispread because they have to make compromise and even sacrifice the healthcare system and human health of the elderly in the name of financial stability avoiding economical catastrophe and unbearable losses. Therefore, the virus of poverty (v_p) is likely going to cause more harm than the COVID-19 one if mathematical evaluation of the situation is avoided or neglected from modeling of sub-systems from the first level. Deeper deep details about building the modeling strategy and procedure can be found in our recent works published elsewhere [14, 29, 43]. Hence, the scientists are reaching the optimization procedure where multifunctional optimization with constrains must be applied and the objective function must include criteria taking into account information from HL I, HL II and HL III.

The epidemiological strategy to avoid infection and spreading of COVID-19 disease is also connected with employment workforce, economy, business, travel, transportation and everything which is required for execution of human activity to obtain added value goods and services. The new 8-coordinate system already changed many established strategies about the employment. A new feature appeared – the so called working place at home that is very positive, and very surprisingly, it is not widely applied in the world. This feature will be studied and developed in the future and it is the so called "hybrid working place". It means, all big cities every single day faced the problem of transportation of millions of working people from home to the companies, offices, research institutes, universities, factories etc. This new life circumstance demonstrates that every human activity which is possible to be executed from home by using modern computer frameworks and facilities must be applied. This not only is saving tremendous amount of money, but most importantly is protecting people by executing the perfect social distance policy. We are sure that this phenomenon will be studied in detail and will be applied sooner or later in its full scale.

Of course, human society will face new problems arising from lack of social contacts, but there are many ways to solve it by introducing new social activities. Transportations and travel will be modified in order to meet the new reality. And once again it will be on the base of our knowledge about the COVID-19 or other pandemic. As conclusions from this hierarchic level, first, one must realize that nothing can be done separately without taking into account the complexity of the human life in new 8-coordinate system conditions. Secondly, scientists from all subjects who are able to clarify the "black box" of any sub-system and make it a "grey" and

"white box" (in term of process control) must do it in collaboration with mathematicians and modelers. And must do it fast because any delay now is paid by loss of human life.

Once again, optimization of human life under COVID-19 pandemic cannot be a choice between SARS-CoV-2 (v_c), "virus" of poverty (v_p) and "virus" of chronic disease (v_{cd}) coordinates. Hence, constraints in optimization procedure include first and foremost strong healthcare limits and restrictions and secondly economical ones. The objective function based on the complex medical-epidemiological-economical criterion, where all control parameters and other constraints are determined by taking knowledge from HL I and HL II, will serve to find and ensure optimal health, social and economic protection.

The World Health Organization (WHO) and the International Monetary Fund (IMF), evidenced that there is a "false dilemma" (controlling the virus and saving lives vs. saving the economy), especially for emerging markets and developing countries where the informal income based on daily wages are preponderant making the social distancing measures impractical. In fact, a much more complex analysis must be performed aiming to solve both problems mutually, since one impacts the other [12].

Of course, no one could underestimate the role of statistical methods during investigation of different hierarchic levels. The statistical approaches are very well developed and some of them are very robust even when experimental data are scarce. At this time, fast information and robust results are required from virologists, molecular biologists, infectologists, microbiologists, biologists, immunologists, etc. (i.e., from all scientists involved in studying the subsystems from HL I, HL III). This is possible by applying innovative modeling and statistical methods to design accurate biological experiments – *in vitro*, *in vivo* and clinical trials. Finally, the scientific approach is the only way to build a winning strategy aiming to save and protect human society in this dangerous time.

Third hierarchic level (HL III): Countermeasure initiatives – financial & monetary assistance, vaccine & drugs R&D and healthcare

The monetary policy worldwide is addressed first to serve the sub-systems in the third hierarchic level where money is needed urgently for research, disease diagnostics, therapies, vaccines, etc. It must be noted, that without robust testing to evaluate the present status and distribution of the infection from COVID-19, it is impossible to observe the scale of pandemic system, and consequently, to control adequately the spread of infection and to improve epidemiological strategy.

An economic response policy worldwide response is obligatory because of the severe socioeconomic consequences of COVID-19 pandemic. In order to make the monetary sub-system working, every step of financial support to affected businesses must be taken. A coordinated financial strategy is necessary to deal with health emergency needs, to support economic activity and to prepare the ground for the recovery of the society. This strategy can ONLY be built considering the knowledge from HL I, HL II and HL III. Time frame of initiatives should include short, medium and long-term activities.

The financial experts must provide objective analysis to the political leaders and the latter will proceed with the complex actions and outline and realize a coordinated economic response.

Significant financial resources should be directed to strengthen the healthcare sector and civil protection mechanisms, and to support affected workers and economic sectors in order to fight the virus of poverty. This is unavoidable. Furthermore, the Ministry of Finance has to be ready to take further measures according to the pandemic situation and current circumstances. As we mentioned, developments of supporting strategies depend exclusively on countries financial resources and external banks solidarity.

Monetary policy: The national banks must support liquidity and financing conditions to households and businesses which will help to ensure the smooth provision of credits to the economy. These measures are aimed at ensuring that all sectors of the economy can benefit from supportive financing conditions that enable them to overcome the COVID-19 shock.

Financial stability: The guidance provided by supervisory authorities to financial institutions under current exceptional circumstances must rely on capital buffers in order to overcome the financing pressures faced by firms and households. Monitoring the pandemic situation is obligatory to control the impact of COVID-19 on society.

Emergency support: Financial emergency grants must be available to first and foremost reinforce the healthcare sub-system. This solidarity instrument will help the efforts to return to a normal functioning of society and economy and will ensure sustainable growth.

Recovery funds: The leaders must discuss legal and practical aspects of such a fund with economists, businessmen, and experts in order to apply innovative financial instruments.

The economic recovery of the society is a real challenge under COVID-19 pandemic and require discussion on many levels for smooth transition in this HL III.

Fourth hierarchic level (HL IV): Other highly influencing social frameworks – religion, media, laws and justice system

Analyzing the fourth hierarchic level (HL IV) of the $LHSC_{19}$ system, it has to be noticed that this level has tremendous responsibility because the broadcasted news, suggestions and hypotheses influence significantly the attitude and life of billions of people.

Role of laws, constitutions and justice: In halls of power across the world, the growing novel coronavirus pandemic of COVID-19 has sometimes been used to stretch, bend or ignore established law and policy. Fundamental freedoms, privacy protections and access to justice have been curtailed in the name of public safety, with legal justifications ranging from appropriate to patently inaccurate. This is because every day the virus takes human lives no matter how much time is needed for thinking and discussing in order to minimize the errors applying laws, constitution and justice.

Role of all religions during pandemic: This sub-system deals with the group of humans with obsessed mentality. In the new life, unfortunately the facts showed that religions have not realized their crucial role in supporting the spiritually engaged groups of people and individuals. It is a well-known truth, that the unknown comes with fear even more if it is a danger. Hence, the religions did NOT understand that during the quarantine they must daily and methodically pray for saving our souls, give faith, hope and love to the laity, emphasize to them every day that we are all on one side of the barricade and God sent us this test to check how

much we are unified. And if he loses the hesitants he will lose the strong and determined. If the poor loses, the rich will lose, as well. And if we abandon the sick, we will abandon the healthy. This has not been seen to date worldwide. Psychologists are not sufficient to deal and overcome the post-traumatic stress after COVID-19 pandemic in this group of people.

Role of all media during pandemics: Journalists were totally confused in the new life and intensified the resonance of panic and chaos with fake news. They took facts from the context (and how to assess the complexity of the behavior of the 8-coordinate system?) pushed to the wall the nation's rescuers, such as Executive authority, Council of Ministers, the Minister of Health, and all the decision makers and leaders responsible for prevention of infection and spread into highly dense municipalities, cities and public places. The information transmitted in public space was very often misleading and most often created an image of leaders worldwide as serial killers. This was achieved by taking the facts out of the scientific context by questioning manipulative, misleading, offensive and often absurd questions. Scientists did not blame anybody of them. Journalists are ignorant just like all of us in this complex and new unique situation. Nobody can control the system if it is not observable and known! The responsibility of journalists during quarantine and pandemic life consists in careful filtration of non-scientifically grounded facts, suggestions, assumptions etc. It is obligatory to finish the news with optimism and hope. That is all the society needs during natural disasters, pandemics and wars, because common sense has always won, and because scientists ALWAYS have been solving issues that are socially important and urgent. It must be noticed that the journalists are not decision makers, therefore they are not paying for their errors, but they spread chaos and fear allowing distribution of fake news. Journalists widely spread the thesis that scientists cause panic in society. Panic is internal state of the human that occurs in the souls of most people when the facts present high danger with unknown consequences.

In conclusion, the crucial responsibility of journalist in the time of COVID-19 pandemic is to calm down the society and to provoke high level of unity and solidarity. Let's cordially remind, that there is NO truth. There is point of view based on the facts. And when the points of view are enough to clarify and represent many and controversial facts, we are able to reach the high truth.

Therefore, the new COVID-19 pandemic life framework (within the 8-coordinate hierarchical system) evidences a new world leader, the Scientists and all the people from the front line. The journalist must show this in a very honest, cordial, sincere and respectful way.

Crucial figures of action

Scientists, researchers, experts (Sc) – the first line medical staff and workers Everyone realized the saving role of scientists at a time when "To be or not to be" concerns each one of us.

As never before, humanity is on one side of the barricade and on the other side stands a powerful, invisible, insidious and ruthless enemy. And the world has shown who really is the new informal leader and savior of the world. All a scientist needs in a pandemic is to understand the phenomena and nature of this disease in order to solve the problems related to them and direct them for the benefit and well-being of society. The urgent task of the pandemic is to create a vaccine and drugs against SARS-CoV-2. But the scientists cannot do it alone, their hands, feet and hearts are the quiet and dedicated heroes on the front line! A true scientist does not need fame, honor, or adoration. All that is enough for him is to see that the human health is not anymore in danger. And here, we come to the role of leaders and decision makers of each country to find the winning way and as soon as possible to apply the scientific discoveries on diseases, to secure, motivate and coordinate the efforts of people from the front line.

Government leaders, politicians (L) – procedure of making of decisions

At the beginning of COVID-19 pandemic, in many countries a complete panic and chaos appeared in the behavior and decisions of politicians who did not realize that they are no longer in full power to control the society and social life. For some time, they did not realize that they could no longer make authoritarian decisions in the new reality of life. These circumstances require from them to be highly responsible executors, which by no means take them down in the lower level of responsibility in solving the effects and consequences of COVID-19.

Nevertheless, scientists cannot blame in full power the decision makers, because the pandemic came to people as a hurricane where unknowns were much more than expected and the application of the method of **trial and error** and the **principles of analogy** at the beginning failed. The accumulated knowledge database and current clinical data on these diseases were zero then, no vaccine was and still is accessible. No drugs were available as well. The brutality of the problem in every infected country that every day the disease took lives. Humans were in a global war where the attack was severe.

On the other hand, phrases such as "another mild flu" or "everything is under control", fatal neglect and hiding the facts have led to thousands of victims around the world.

Politicians wondered what to choose between COVID-19 spread and the poverty virus (which is ravaging industry and business), completely ignoring the seventh and eighth coordinates, but as we showed the system is too complex to be controlled because at the beginning it was not observable and known.

Hence, the reproach to some politicians was and is that they did not choose the health of the people first, but took more care of their image, advertising to the public, how hard will life be in case of economic collapse. Now, as never before, humans are all one creature, one body, one pain and one life. Globalization of human society shows this as well as and the $LHSC_{19}$.

Many voices of politicians and decision makers called for planned action in public life. How it that possible when the behavior of the complex system (8-coordinate) is not observable, rather unknown. The first condition for the control and management of any system is its observability.

<u>Popular example</u>: close your eyes and ride a bike, car, motorcycle, boat, bus, etc. The only adequate management of any sub-system (Fig. 1) with many unknowns at the moment is based on the trial and error method and the principles of analogy based on the accumulated knowledge database and current clinical data. This will continue until a vaccine and medicine (drugs) against the SARS-CoV-2 pathogen will be developed. Then, it will be possible to describe this 8-coordinate system including all interactions and relationships between the sub-systems. And only then, the distribution of the poverty virus ($v_p = f(v_c)$) will be defeated. The solidarity in new time is unavoidable.

On the basis of the above, it must be highlighted that several of the coordinates (i.e., variables) are interrelated or even mutually dependent along all of hierarchical levels and their sub-

systems. Therefore, several dependence equations between such variables can be expressed (see Eqs. (2)-(6)):

$$v_c = f(x, y, z, t, v_p, Sc, L(Sc)),$$
 (2)

$$v_p = f(x, y, z, t, v_c, Sc, L(Sc)),$$
 (3)

$$v_{cd} = f(x, y, z, t, v_p, Sc, L(Sc)),$$
 (4)

$$Sc = f(x, y, z, t), \tag{5}$$

$$L = f(x, y, z, t, Sc).$$
(6)

The dependence between the Scientists and first line staff (Sc) and the Government Leaders and Decision Makers (L(Sc)) must be highlighted. The first, as the key players combating all problems associated to COVID-19 are dedicated to the research for a definitive solution. The second are to provide adequate and prompt conditions and to rely on the Scientists' knowledge. There is no way but the fine alignment of these two crucial agents to achieve this urgent and worldwide common goal.

Conclusion

Life of human society during the COVID-19 pandemic was described by using the principal of analogy from technical sciences whereby system analysis was applied to distinguish four hierarchic levels of human life. Moreover, the new life can be characterized as a system which is a function of 8 coordinates such as follows: 4 everlasting coordinates – three for space and one for time measurement and the new 4 coordinates: coronavirus, "virus" of poverty, "virus" of chronically ill people and scientists as a new leader of the world. Analysis of human life in the new framework has been done in details where sub-systems, mathematical description and their interactions need to be determined as soon as possible in order to serve to political leaders and decision makers to control the pandemic and especially to monitor and control the "virus" of poverty not only in one specific country but for the well-being of the whole world. The authors do believe that this manuscript will be extremely useful particularly to stop panic and chaos caused by an unprecedented and fierce enemy such as the coronavirus disease COVID-19. Further, this analysis can be extremely useful to the leaders and politicians in the future, where possible even more dangerous scenarios are not excluded.

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References

- 1. Andersen K.G., Rambaut A., Lipkin W.I., Holmes E.C., Garry R.F. (2020). The Proximal Origin of SARS-CoV-2, Nature Medicine, 26, 450-452.
- 2. Bagdonaite I., Wandall H.H. (2018). Global Aspects of Viral Glycosylation, Glycobiology, 28, 443-467.

- 3. Belouzard S., Chu V.C., Whittaker G.R. (2009). Activation of the SARS Coronavirus Spike Protein via Sequential Proteolytic Cleavage at Two Distinct Sites, Proceedings of the National Academy of Sciences, 106, 5871-5876.
- 4. Belouzard S., Millet J.K., Licitra B.N., Whittaker G.R. (2012). Mechanisms of Coronavirus Cell Entry Mediated by the Viral Spike Protein, Viruses, 4, 1011-1033.
- 5. Bosch B.J., van der Zee R., de Haan C.A.M., Rottier P.J.M. (2003). The Coronavirus Spike Protein is a Class I Virus Fusion Protein: Structural and Functional Characterization of the Fusion Core Complex, Journal of Virology, 77, 8801-8811.
- 6. Channappanavar R., Zhao J., Perlman S. (2014). T Cell-mediated Immune Response to Respiratory Coronaviruses, Immunologic Research, 59, 118-128.
- 7. Chen Y., Guo Y., Pan Y., Zhao Z.J. (2020). Structure Analysis of the Receptor Binding of 2019-nCoV, Biochemical and Biophysical Research Communications, 525, 135-140.
- Croxford A.L., Lanzinger M., Hartmann F.J., Schreiner B., Mair F., Pelczar P., Clausen B.E., Jung S., Greter M., Becher B. (2015). The Cytokine GM-CSF Drives the Inflammatory Signature of CCR2+ Monocytes and Licenses Autoimmunity, Immunity, 43, 502-514.
- Fang M., Siciliano N.A., Hersperger A.R., Roscoe F., Hu A., Ma X., Shamsedeen A.R., Eisenlohr L.C., Sigal L.J. (2012). Perforin-dependent CD4+ T-cell Cytotoxicity Contributes to Control a Murine Poxvirus Infection, Proceedings of the National Academy of Sciences, 109, 9983-9988.
- Follis K.E., York J., Nunberg J.H. (2006). Furin Cleavage of the SARS Coronavirus Spike Glycoprotein Enhances Cell-cell Fusion but does not Affect Virion Entry, Virology, 350, 358-369.
- Fujimoto I., Pan J., Takizawa T., Nakanishi Y. (2000). Virus Clearance through Apoptosisdependent Phagocytosis of Influenza A Virus-infected Cells by Macrophages, Journal of Virology, 74, 3399-3403.
- Georgieva K., Ghebreyesus T.A. (2020). Some Say There Is a Trade-off: Save Lives or Save Jobs – This is a False Dilemma, <u>https://www.imf.org/en/News/Articles/2020/04/03/</u> <u>vs-some-say-there-is-a-trade-off-save-lives-or-save-jobs-this-is-a-false-dilemma</u> (access date 11 March 2021).
- 13. Hamming I., Timens W., Bulthuis M., Lely A., Navis G., van Goor H. (2004). Tissue Distribution of ACE2 Protein, the Functional Receptor for SARS Coronavirus. A First Step in Understanding SARS Pathogenesis, The Journal of Pathology, 203, 631-637.
- Hinterholz C.L., Trigueros D.E.G., Módenes A.N., Borba C.E., Scheufele F.B., Schuelter A.R., Kroumov A.D. (2019). Computational Fluid Dynamics Applied for the Improvement of a Flat-plate Photobioreactor towards High-density Microalgae Cultures, Biochemical Engineering Journal, 151, 107257.
- Hoffmann M., Kleine-Weber H., Schroeder S., Krüger N., Herrler T., Erichsen S., Schiergens T.S., Herrler G., Wu N.-H., Nitsche A., Müller M.A., Drosten C., Pöhlmann S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor, Cell, 181, 271-280.e8.
- 16. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., Xie X., Yin W., Li H., Liu M., Xiao Y., Gao H., Guo L., Xie J., Wang G., Jiang R., Gao Z., Jin Q., Wang J., Cao B. (2020). Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China, The Lancet, 395, 497-506.
- 17. Huang H., Wang S., Jiang T., Fan R., Zhang Z., Mu J., Li K., Wang Y., Jin L., Lin F., Xia J., Sun L., Xu B., Ji C., Chen J., Chang J., Tu B., Song B., Zhang C., Wang F.-S., Xu R. (2019). High Levels of Circulating GM-CSF+CD4+ T Cells are Predictive of Poor

Outcomes in Sepsis Patients: A Prospective Cohort Study, Cellular & Molecular Immunology, 16, 602-610.

- Jeffers S.A., Tusell S.M., Gillim-Ross L., Hemmila E.M., Achenbach J.E., Babcock G.J., Thomas W.D., Thackray L.B., Young M.D., Mason R.J., Ambrosino D.M., Wentworth D.E., DeMartini J.C., Holmes K.V. (2004). CD209L (L-SIGN) is a Receptor for Severe Acute Respiratory Syndrome Coronavirus, Proceedings of the National Academy of Sciences, 101, 15748-15753.
- Jia H.P., Look D.C., Shi L., Hickey M., Pewe L., Netland J., Farzan M., Wohlford-Lenane C., Perlman S., McCray P.B. (2005). ACE2 Receptor Expression and Severe Acute Respiratory Syndrome Coronavirus Infection Depend on Differentiation of Human Airway Epithelia, Journal of Virology, 79, 14614-14621.
- 20. Kaffarov V.V., Vinarov A.J., Gordeev L.S. (1979). Modeling Biochemical Reactors, Lesnaya Promishlenost, Publisher Forrest Industry, Moscow (in Russian).
- 21. Kaffarov V.V., Vinarov A.J., Gordeev L.S. (1985). Modeling and System Analysis of Biochemical Industrial Production, Lesnaya Promishlenost, Publisher Forrest Industry, Moscow (in Russian).
- 22. Koutsogiannaki S., Shimaoka M., Yuki L. (2019). The Use of Volatile Anesthetics as Sedatives for Acute Respiratory Distress Syndrome, Translational Perioperative and Pain Medicine, 6, 27-38.
- 23. Kroumov A.D., Dimitrov D., Gordeev L. (1991). Prediction of the Functioning of a Cell Bioreactor Model for Purification of Industrial Effluents, Bioautomation, 9, 11-18 (in Russian).
- 24. Kroumov A.D., Gacheva G., Iliev I., Alexandrov S., Pilarski P., Petkov G. (2013). Analysis of Sf/V Ratio of Photobioreactors Linked with Algal Physiology, Genetics and Plant Physiology, 3, 1-2.
- 25. Kroumov A.D., Gordeev L., Vinarov, A. (1987). Scale-up of Loop Reactor on the Basis of Full Mathematical Model of the Biosynthesis Process, Proc Uni Russ Chem Chem Technol, 30, 101-106 (in Russian).
- 26. Kroumov A.D., Gordeev L. (1988). A Mathematical Model of the Biosynthesis Process and Parametrical Sensitivity of the Column Fermenter, Bioautomation, 5, 3-7 (in Russian).
- 27. Kroumov A.D., Módenes A.N., Tait M.C.D.A. (2006). Development of New Unstructured Model for Simultaneous Saccharification and Fermentation of Starch to Ethanol by Recombinant Strain, Biochemical Engineering Journal, 28, 243-255.
- 28. Kroumov A.D., Módenes A.N., Trigueros D.E.G. (2015). A Complex Theoretical Approach for Algal Medium Optimization for CO₂ Fixation from Flue Gas, Acta Microbiologica Bulgarica, 31, 61-70.
- Kroumov A.D., Módenes A.N., Trigueros D.E.G., Espinoza-Quiñones F.R., Borba C.E., Scheufele F.B., Hinterholz C.L. (2016). A Systems Approach for CO₂ Fixation from Flue Gas by Microalgae – Theory Review, Process Biochemistry, 51, 1817-1832.
- Kroumov A.D., Módenes A.N., Wenzel B.M. (2007). Development of the Enzymatic Kinetics Model of Vegetable Oils Transesterification for Biodiesel Production, Acta Scientiarum Technology, 29, 9-16 (in Portuguese).
- 31. Kroumov A.D., Scheufele F.B., Trigueros D.E.G., Modenes A.N., Zaharieva M., Najdenski H. (2017). Modeling and Technoeconomic Analysis of Algae for Bioenergy and Coproducts, In: Algal Green Chem, Elsevier, 201-241.
- Letko M., Marzi A., Munster V. (2020). Functional Assessment of Cell Entry and Receptor Usage for SARS-CoV-2 and Other Lineage B Betacoronaviruses, Nature Microbiology, 5, 562-569.
- 33. Li W., Moore M.J., Vasilieva N., Sui J., Wong S.K., Berne M.A., Somasundaran M., Sullivan J.L., Luzuriaga K., Greenough T.C., Choe H., Farzan M. (2003). Angiotensin-

converting Enzyme 2 is a Functional Receptor for the SARS Coronavirus, Nature, 426, 450-454.

- 34. Liu S., Su X., Pan P., Zhang L., Hu Y., Tan H., Wu D., Liu B., Li H., Li H., Li Y., Dai M., Li Y., Hu C., Tsung A. (2016). Neutrophil Extracellular Traps are Indirectly Triggered by Lipopolysaccharide and Contribute to Acute Lung Injury, Scientific Reports, 6, 37252.
- 35. Lovren F., Pan Y., Quan A., Teoh H., Wang G., Shukla P.C., Levitt K.S., Oudit G.Y., Al-Omran M., Stewart D.J., Slutsky A.S., Peterson M.D., Backx P.H., Penninger J.M., Verma S. (2008). Angiotensin Converting Enzyme-2 Confers Endothelial Protection and Attenuates Atherosclerosis, The American Journal of Physiology: Heart and Circulatory Physiology, 295, H1377-H1384.
- 36. Marzi A., Gramberg T., Simmons G., Möller P., Rennekamp A.J., Krumbiegel M., Geier M., Eisemann J., Turza N., Saunier B., Steinkasserer A., Becker S., Bates P., Hofmann H., Pöhlmann S. (2004). DC-SIGN and DC-SIGNR Interact with the Glycoprotein of Marburg Virus and the S Protein of Severe Acute Respiratory Syndrome Coronavirus, Journal of Virology, 78, 12090-12095.
- 37. Millet J.K., Whittaker G.R. (2014). Host Cell Entry of Middle East Respiratory Syndrome Coronavirus after Two-step, Furin-mediated Activation of the Spike Protein, Proceedings of the National Academy of Sciences, 111, 15214-15219.
- Monte Blanco S.P.D., Scheufele F.B., Módenes A.N., Espinoza-Quiñones F.R., Marin P., Kroumov A.D., Borba C.E. (2017). Kinetic, Equilibrium and Thermodynamic Phenomenological Modeling of Reactive Dye Adsorption onto Polymeric Adsorbent, Chemical Engineering Journal, 307, 466-475.
- 39. Nao N., Yamagishi J., Miyamoto H., Igarashi M., Manzoor R., Ohnuma A., Tsuda Y., Furuyama W., Shigeno A., Kajihara M., Kishida N., Yoshida R., Takada A. (2017). Genetic Predisposition to Acquire a Polybasic Cleavage Site for Highly Pathogenic Avian Influenza Virus Hemagglutinin, MBio, 8, 1-15.
- 40. Ou X., Liu Y., Lei X., Li P., Mi D., Ren L., Guo L., Guo R., Chen T., Hu J., Xiang Z., Mu Z., Chen X., Chen J., Hu K., Jin Q., Wang J., Qian Z. (2020). Characterization of Spike Glycoprotein of SARS-CoV-2 on Virus Entry and Its Immune Cross-reactivity with SARS-CoV, Nature Communications, 11, 1620.
- 41. Qin C., Zhou L., Hu Z., Zhang S., Yang S., Tao Y., Xie C., Ma K., Shang K., Wang W., Tian D.-S. (2020). Dysregulation of Immune Response in Patients with Coronavirus 2019 (COVID-19) in Wuhan, China, Clinical Infectious Diseases, 53, 1-30.
- 42. Rabi F.A., Al Zoubi M.S., Kasasbeh G.A., Salameh D.M., Al-Nasser A.D. (2020). SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far, Pathogens, 9, 231.
- Scheufele F.B., Hinterholz C.L., Zaharieva M.M., Najdenski H.M., Módenes A.N., Trigueros D.E.G., Borba C.E., Espinoza-Quiñones F.R., Kroumov A.D. (2019). Complex Mathematical Analysis of Photobioreactor System, Engineering in Life Sciences, 19, 844-859.
- 44. Sheahan T., Rockx B., Donaldson E., Sims A., Pickles R., Corti D., Baric R. (2008). Mechanisms of Zoonotic Severe Acute Respiratory Syndrome Coronavirus Host Range Expansion in Human Airway Epithelium, Journal of Virology, 82, 2274-2285.
- 45. Sluimer J., Gasc J., Hamming I., van Goor H., Michaud A., van den Akker L., Jütten B., Cleutjens J., Bijnens A., Corvol P., Daemen M., Heeneman S. (2008). Angiotensinconverting Enzyme 2 (ACE2) Expression and Activity in Human Carotid Atherosclerotic Lesions, The Journal of Pathology, 215, 273-279.
- 46. Small B.A., Dressel S.A., Lawrence C.W., Drake D.R., Stoler M.H., Enelow R.I., Braciale T.J. (2001). CD8+ T Cell-mediated Injury *in vivo* Progresses in the Absence of Effector T Cells, Journal of Experimental Medicine, 194 1835-1846.

- 47. Tian S., Hu W., Niu L., Liu H., Xu H., Xiao S.-Y. (2020). Pulmonary Pathology of Earlyphase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients with Lung Cancer, Journal of Thoracic Oncology, 15, 700-704.
- 48. Trigueros D.E.G., Módenes A.N., Kroumov A.D., Espinoza-Quiñones F.R. (2010). Modeling of Biodegradation Process of BTEX Compounds: Kinetic Parameters Estimation by Using Particle Swarm Global Optimizer, Process Biochemistry, 45, 1355-1361.
- 49. Walls A.C., Park Y.-J., Tortorici M.A., Wall A., McGuire A.T., Veesler D. (2020). Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein, Cell, 181, 281-292.e6.
- 50. Wan Y., Shang J., Graham R., Baric R.S., Li F. (2020). Receptor Recognition by the Novel Coronavirus from Wuhan: An Analysis Based on Decade-long Structural Studies of SARS Coronavirus, Journal of Virology, 94, 1-9.
- 51. Wang M., Hao H., Leeper N.J., Zhu L. (2018). Thrombotic Regulation from the Endothelial Cell Perspectives, Arteriosclerosis, Thrombosis, and Vascular Biology, 38, e90-e95.
- 52. Wenzel B., Tait M., Módenes A., Kroumov A. (2006). Modelling Chemical Kinetics of Soybean Oil Transesterification Process for Biodiesel Production: An Analysis of Molar Ratio between Alcohol and Soybean Oil Temperature Changes on the Process Conversion Rate, International Journal Bioautomation, 5, 13-22.
- 53. Wrapp D., Wang N., Corbett K.S., Goldsmith J.A., Hsieh C.-L., Abiona O., Graham B.S., McLellan J.S. (2020). Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation, Science, 367, 1260-1263.
- 54. Xu Z., Shi L., Wang Y., Zhang J., Huang L., Zhang C., Liu S., Zhao P., Liu H., Zhu L., Tai Y., Bai C., Gao T., Song J., Xia P., Dong J., Zhao J., Wang F.-S. (2020). Pathological Findings of COVID-19 Associated with Acute Respiratory Distress Syndrome, The Lancet Respiratory Medicine, 8, 420-422.
- 55. Yang Z.-Y., Huang Y., Ganesh L., Leung K., Kong W.-P., Schwartz O., Subbarao K., Nabel G.J. (2004). pH-dependent Entry of Severe Acute Respiratory Syndrome Coronavirus is Mediated by the Spike Glycoprotein and Enhanced by Dendritic Cell Transfer through DC-SIGN, Journal of Virology, 78, 5642-5650.
- 56. Yoshikawa T., Hill T., Li K., Peters C.J., Tseng C.-T.K. (2009). Severe Acute Respiratory Syndrome (SARS) Coronavirus-Induced Lung Epithelial Cytokines Exacerbate SARS Pathogenesis by Modulating Intrinsic Functions of Monocyte-derived Macrophages and Dendritic Cells, Journal of Virology, 83, 3039-3048.
- 57. Young R.E., Thompson R.D., Larbi K.Y., La M., Roberts C.E., Shapiro S.D., Perretti M., Nourshargh S. (2004). Neutrophil Elastase (NE)-deficient Mice Demonstrate a Nonredundant Role for NE in Neutrophil Migration, Generation of Proinflammatory Mediators, and Phagocytosis in Response to Zymosan Particles *in vivo*, Journal of Immunology, 172, 4493-4502.
- 58. Zeng H., Pappas C., Belser J.A., Houser K.V., Zhong W., Wadford D.A., Stevens T., Balczon R., Katz J.M., Tumpey T.M. (2012). Human Pulmonary Microvascular Endothelial Cells Support Productive Replication of Highly Pathogenic Avian Influenza Viruses: Possible Involvement in the Pathogenesis of Human H5N1 Virus Infection, Journal of Virology, 86, 667-678.
- 59. Zheng M., Gao Y., Wang G., Song G., Liu S., Sun D., Xu Y., Tian Z. (2020). Functional Exhaustion of Antiviral Lymphocytes in COVID-19 Patients, Cellular & Molecular Immunology, 17, 533-535.
- 60. Zhou P., Lou Yang X., Wang X.G., Hu B., Zhang L., Zhang W., Si H.R., Zhu Y., Li B., Huang C.L., Chen H.D., Chen J., Luo Y., Guo H., Di Jiang R., Liu M.Q., Chen Y., Shen X.R., Wang X., Zheng X.S., Zhao K., Chen Q.J., Deng F., Liu L.L., Yan B.,

Zhan F.X., Wang Y.Y., Xiao G.F., Shi Z.L. (2020). A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin, Nature, 579, 270-273.

- Zhou Y., Fu B., Zheng X., Wang D., Zhao C., Qi Y., Sun R., Tian Z., Xu X., Wei H. (2020). Pathogenic T-cells and Inflammatory Monocytes Incite Inflammatory Storms in Severe COVID-19 Patients, National Science Review, 7(6), 998-1002.
- 62. Zou X., Chen K., Zou J., Han P., Hao J., Han Z. (2020). Single-cell RNA-seq Data Analysis on the Receptor ACE2 Expression Reveals the Potential Risk of Different Human Organs Vulnerable to 2019-nCoV Infection, Frontiers in Medicine, 14, 185-192.

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