Psychiatria Danubina, 2021; Vol. 33, Suppl. 4, pp 402-413 *Conference paper*
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Review

COMORBIDITIES AND SYNDEMICS IN THE COVID-19 AGE: CHALLENGES AND OPPORTUNITIES FOR BRINGING SEPARATED BRANCHES OF MEDICINE CLOSER TO EACH OTHER

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SUMMARY

The Corona Virus Disease 2019 (COVID-19) as a unique disaster has stressed the extreme importance of the three issues for medicine, society and humanity in general: comorbidity, pandemic and syndemic. There are many reasons why the study of comorbidities and syndemics of COVID-19 is of great importance for researchers, clinicians and health policy makers who are responsible for health care organization and funding in a bid to develop more effective and efficient prevention and treatment. Thinking about COVID-19 through a syndemics concept and taking biological, psychological, social and spiritual dimensions into account, physicians could be more effective in clinical practice and community-based interventions. The outcome of SARS-CoV-2 infection is determined by the virus-host interaction, with pathogenicity of SARS-CoV-2 being related to the presence of comorbid diseases. The risk for severe COVID-19 clinical manifestations and death increases with age of patients and comorbidity. General mechanisms of multi-system dysfunction and multi-organ damage reported in COVID-19 are probably related to ubiquitous expression of ACE2 in many tissues and its important role in the renin-angiotensin-aldosterone system (RAAS) functioning. Physicians all over the world should be aware of COVID-19 related comorbidities, multisystem disorders and syndemics, as well as treatment and preventive strategies. COVID-19 age is a right time to reconsider the state of science and practice in comorbidity medicine field from the both epistemological and treatment perspective. Comorbidities and multimorbidities are indifferent to medical specializations, so the integrative and complementary medicine is an imperative in the both education and practice. Shifting the paradigm from vertical and mono-morbid interventions to comorbidity, multimorbidity and multi-system disease approaches enhances effectiveness and efficiency of human resources utilization. The aim of this review is to summarize the theoretical concepts and clinical experience and research regarding comorbidity in general, and specifically related to the COVID-19 pandemic, syndemics and infodemic.

Key words: *comorbidity - multimorbidity - epigenetics - SARS-CoV-2 - COVID-19 - multi-system disorders - diseases interactions - syndemics*

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INTRODUCTION

By February 2021 the Corona Virus Disease 2019 (COVID-19) has reached the dimensions of a global disaster that shook our world with 107 million people suffering from the disease and more than two million three hundred dead worldwide (WHO 2021). The COVID-19 pandemic has attracted attention to three major challenges for medicine, society and humanity in general: comorbidity (polypathy), syndemics and infodemics. The fact that some disorders and diseases occur together more frequently than it would be expected by chance opens doors to the exploration of factors of pathogenesis of the diseases involved, what is an extremely important issue in person-centered and personalized medicine. The prevalence of comorbidity has increased rapidly and continues to grow for many reasons, including the increase of life expectancy, changes in life style, rapid urbanization, environmental changes and pollution, iatrogenesis, and fragmentation of medical services (Sartorius et al. 2015). Although we are learning every day more and more about COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), member of the 2B group of beta-corona virus family, huge gaps in knowledge still exist. SARS-CoV-2 is characterized by high resilience to the conditions outside the body and in the body fluids. It uses "Trojan horse" strategy to hide viral material within exosomes or extracellular vesicles during the "silence time" what may result in the re-appearance of the viral RNA in the recovered COVID-19 patients (see Elrashdy et al. 2020). In the last 100 years, the world did not face a dangerous infective pandemic such as the COVID-19 pandemic. The COVID-19 dark triadics pandemic, syndemic and infodemic are a paramount challenge to contemporary medicine and human society in general. Russian president Vladimir Putin has warned that the world risks sliding deeper into instability and a possible end of civilization because the COVID-19 pandemic combined with global rivalries and international tension could turn the world into a 'dark anti-Utopia" (Daily Mail 2021).

COVID-19 comorbidities and syndemics can be metaphorically described as the rock on which many fine theories are wrecked and upon which better ones followed by efficient clinical practice can be built. There is an urgent need for better understanding the coexistence of various or similar diseases in the same patient, comorbidity, multimorbidity, polypathy, multisystem diseases and syndemics in a bid to develop more

effective and efficient prevention and treatment. With regards to these phenomena epistemology raises many conceptual and explanatory questions in nosotropic, etiotropic and treatment frameworks (Jakovljevic & Crncevic 2012). Studies have indicated that a number of condition and diseases including non-communicable diseases (NCDs) such as diabetes, obesity, arterial hypertension, cardiovascular disease and lung disease present risk factors for COVID-19 infection. The higher mortality rates are also being reported in COVID-19 patients with those and other NCDs (Singh 2020). Patients with COVID-19 comorbid with other disorders have a significantly worse clinical outcome than those without comorbidity. A comprehensive clinical evaluation and good management of comorbidity on the other hand results in significantly better outcome of treatment.

There are many reasons why the study of comorbidities and syndemics of COVID-19 is of great importance for researchers, clinicians and health policy makers who are responsible for health care organization and funding. Conventional approaches to diseases involved in comorbidity in medicine and public health programs commonly miss and fail to control the powerful joint effects of medical, ecological, socio-cultural, psychological, economic, and political factors. The challenge before medicine now is to deal with the combination of systemic infection and viral multi-tropism, environmental distress, comorbid diseases and negative effects of globalization. The ways the SARS-CoV-2 interacts with our body-mind systems and the pathophysiological scenarios for different clinical presentations in the acute phase of the COVID-19 and long-lasting outcomes are fundamental questions to be addressed in order to develop medical, epidemiological, social and political treatment strategies. The aim of this paper is to summarize the theoretical concepts, clinical experience and results of research with regards to these issues, to comorbidity in general, and to physical and mental illness related to the COVID-19 syndemic and infodemic.

COMORBIDITY AND MULTIMORBIDITY: MULTIDIMENSIONAL AND MULTI-INTERPRETABLE PHENOMENA BRING SEPARATED BRANCHES OF MEDICINE CLOSER TO EACH OTHER

The term comorbidity has three meanings: 1. two or more medical conditions existing simultaneously but independently in the same individual; 2. two or more medical conditions existing simultaneously and interdependently with each other - meaning that one medical condition causes, is caused, or is otherwise related to another condition in the same individual; 3. two or more medical conditions regardless the causality (see Jakovljevic & Ostojic 2013). Some authors define comorbidity as the simultaneous presence of two or more diseases in some individual which are associated with each other through pathogenic mechanisms and more frequently than it would be expected by chance (the inevitable side) in contrast to multimorbidity which refers to the simultaneous presence of two or more diseases which appear randomly (the accidental side) not having any connection to each other through pathogenic mechanisms (see Aragona 2009, Jakovljevic & Crncevic 2012). There is also an interesting suggestion to use the term comorbidity for the co-occurrence of two or more diseases, the term hypercomorbidity (syntrophias) for the association of two or more diseases at a higher rate than expected by chance, and the term hypocomorbidity instead of the term anticomorbidity (dystropias) for diseases that appear together at a lower rate than expected (see Jakovljevic & Ostojic 2013, Puzyrev 2015).

Several pathways to etiological, casual or concordant comorbidity can be identified in the literature: *shared predisposition and vulnerability* (personality traits and types, joint epi/genetic abnormalities), *shared risk factors* (stress, psycho-trauma, food intolerance, unhealthy life styles, lack of social support, hostile thoughts, negative emotions, pessimism) and *shared mechanisms* (failed or unsuccessful coping, adjustment, resilience or personality defence mechanisms, endocrine and immune disruption, vital exhaustion, disruption of internal healing system, shared gene polymorphism). We have several options how to evaluate, explain and describe simultaneous existence or sequential appearance two or more diseases and illnesses (see table 1). As comorbidity, multi-morbidity and multisystem disease are multi-interpretable phenomena the method of multiple working hypotheses may be useful in theory and clinical practice. As endophenotype is state independent, illness comorbidity as a biomarker is an interesting concept (see Anisman Hayley 2012). Somatic diseases can be markers for subsequent mental illness as well as mental disorders can be markers of developing somatic disease.

Systems network medicine provides new possibilities for better understanding, treatment and prevention of comorbidities. Association and concentration networks consisting of nodes, components of system, and edges, relationships between these components, have become a staple of systems medicine and biology (see Jakovljevic & Jakovljevic 2019, Jones et al. 2019). Comorbidity network analysis (CNA), a graph-theoretic approach, offers insights into disease-disease interactions, etiology and pathogenesis of disease comorbidities as well as it drives development of preventive and therapeutic strategies. The CMA suggests that so-called bridge symptoms may have an important role in the development and maintenance of comorbid diseases. Bridge strength, bridge betweenness, bridge closeness, and bridge expected influence are effective tools to identify symptoms that indicate possible comorbidity (Jones et al. 2019). Possible practical application of the theoretical constructions of diseasomes in the concept of the network management in network systems

Table 1. Types of comorbidity and multimorbidity

Etiological (EC) and non-etiological comorbidity: EC is related to concurrent damage to different organs and mind-body systems, which is caused by a singular pathological agent. Epiphenomenal comorbidity refers to situations where several conditions are associated with one another, it is possible that one of them is just an epiphenomena or product of the other two.

*Primary and secondary disease comorbidity (PSDC)***:** There are three ways of making PSDC distinction: chronological sequence, causal inference (cause and effect) and symptomatic predominance. The PSDC has been generally used to signify cause and consequence between comorbid disorders.

Concurrent (co-occurring, simultaneous) and successive (sequential) comorbidity: The term comorbidity may include several temporal relationships, e.g. life-time comorbidity, simultaneous (intra-episode) and successive comorbidity.

Casual (CC) vs. random (RC) comorbidity: CC describes disease clustering with a pathophysiological relation between the different diseases, e.g. shared risk factors. Cluster comorbidity indicates statistically significant associations between diseases without a casual explanation. RC describes the co-occurrence of diseases by chance.

Undirectional and bidirectional comorbidity. Etiological and casual comorbidity may be undirectional or bidirectional. Direction of comorbidity may be defined as the ratio between the probability of each disease to onset before the other. For example, many patients with coeliac disease suffer from migraine but only a few individuals suffering from migraine are coeliac.

Complicated comorbidity appears as the result of the primary disease or its treatment, and usually subsequent after some time. *Conjugated disease* refers to the complication of the primary disease related to its etiological and pathogenetic factors (the cause of comorbidity). *Iatrogenic comorbidity* appears as negative effect of the treatment.

Trans-syndromal (TS) vs. trans-nosological (TN) comorbidity: TS comorbidity represents coexistence of two or more syndromes pathogenetically related to each other. TN comorbidity denotes coexistence of two or more nosological units pathogenetically related to each other.

Diagnostic (DC) and prognostic (PC) comorbidity: DC is likely whenever diagnostic criteria are based on patterns of symptoms that are individually nonspecific. PC refers to diseases (in relation to an index disease) graded according to their anticipated effects on therapy and life expectancy. Disorders that predispose an individual to develop other disorders and complications have prognostic comorbidity.

Homotypic (HoC) and heterotypic (HeC) comorbidity: HoC refers to disorders within a diagnostic grouping, e.g. major depression and dysthymia. HoC may be a marker of homotypic diseases continuity. HeC refers to disorders from different diagnostic groupings and may be a marker of severity.

Concordant (CoC) vs. discordant (DiC) comorbidity: CoC refers to diseases as parts of the same pathophysiologic risk profile and more likely to share the same management and are more likely to be the focus of the same disease management plan. For example, concordant conditions in patients with diabetes may be either microvascular complications like retinopathy, nephropathy and neuropathy or macrovascular complications like coronary heart disease, cerebrovascular disease. DiC refers to diseases that are not directly related in either pathogenesis or management and do not share an underlying predisposing factor.

Syntropic comorbidity (SynC) or direct comorbidity) vs. Dystrophic comorbidity (DysC) or inverse comorbidity): SynC refers to mutual disposition or attraction of the two or more diseases in the same patient (eg. cardiovascular diseases united into a cardiovascular continuum9. DysC refers to diseases that were rarely fund in the same patient in the same time (tuberculosis and bronchial astma; diabetes type 1 and peptic ulcer, etc.).

medicine is rolling on the horizon. The hub therapy that is aimed at modulation or desintegation of the hubs (the nodes having a high number of edges connected to them and short path length with other nodes) that are involved in syntropic comorbidity is promising concept (see Puzyrev 2015).

Since COVID-19 started to spread all over the world, patients with chronic non-communicable diseases (CNCDs) such as arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), etc. were designated as a particularly vulnerable group of the population. COVID-19 along with previous diseases, commonly chronic NCDs form a vicious circle with higher risks for severe clinical manifestations, complications and mortality. It is important to keep in mind the fact that chronic NCDs, e.g. autoimmune diseases (Liu et al. 2020, Bonek et al. 2021), share some characteristics with infectious diseases such as the dysfunctional innate immune response and the pro-inflammatory mechanisms. The activation of innate immune responses (inflammation) may contribute to the development of mental disorders in medically ill individuals as well as to the development of somatic disorders in mentally ill patients. As pandemic continues to progress clinicians have registered, in addition to SARS-CoV-2 induced pneumonia and

acute respiratory distress syndrome (ARDS), an increasing number of extra-pulmonary manifestations involving multiple organs and physiologic systems such as gastrointestinal, nervous and cardiovascular systems. Some patients after COVID-19 developed autoimmune diseases such as Guillain-Barre disease and systemic lupus erythematosus (Liu et al. 2021).

COVID-19, COMORBIDITIES, DISEASE INTERACTIONS AND SYNDEMICS: SARS-COV-2 MECHANISMS AND MULTI-ORGAN TARGETING

The understanding of the SARS-CoV-2 structure and mechanisms as well as hosts characteristics and reactions should enable a rational, more precise and personalized approach to the development of more effective drugs as well as to more successful prevention and treatment of COVID-19. Angiotensin-Converting Enzyme 2 (ACE2), which is expressed in different organs such as lung, heart, brain, gut, vessels, kidney, spleen and skin, is target receptors for SARS-CoV-2. The interaction of SARS-CoV-2 with angiotensin-converting-enzyme-2 (ACE2) seems to be a key factor for virus infectivity and multi-tropism. Silent information regulator T1 (SIRT1), a histone deacetylase (HDAC) class III regulates ACE2 level (El Baba & Herbein 2020). The so-called cytokine storm mediated by pro-inflammatory TNF, IL-1, IL-6 and interferons is supposed to be one of the key elements of COVID-19 pathogenesis. It results in ARDS worsening and widespread tissue damage with multi-system failure and death (Atlante et al. 2020). The structure of corona virus involves four structural proteins which are important for understanding of COVID-19 pathophysiology: spike (S) protein responsible for virus attachment to the receptor and the fusion with the cell membrane, nucleocapsid (N) protein involved in genome replication and which interacts with viral RNA to form the ribonucleoprotein, envelope (E) protein which helps in virions assembly and comprises ion channel actions; and membrane (M) protein important for the assembly of new virus particles (Atlante et al. 2020). SARS-CoV-2 uses its spike protein S to attach to cells via ACE2 receptor, and enters the cells following cleavage by transmembrane serine protease (TMPRSS2) and furine (see Gold et al. 2020). It seems that the affinity of the S protein is associated with the transmissibility of the SARS-CoV-2 while ACE2 expression levels are associated with susceptibility to SARS-CoV-2 (Li et al. 2021). ACE2 is present in many tissues, the cardiovascular, renal and gastrointestinal tissues, in the brain and testis (Ragia & Manolopoulos 2020), but lung alveolar epithelial cells are considered to be the primary targets for SARS-CoV-2. The host response is a key determinant of the disease severity. Endocytosis of the ACE2-virus complex induces decreased level of ACE2 and reduction in conversion of the vasopressor angiotensin-II to the vasodilatator angiotensin 1-7 (Ang1-7) contributing to lung failure and massive pulmonary fibrosis. ACE2 as an important component of the renin-aldosterone-angiotensin system (RAAS), plays a role in arterial hypertension while ACE-inhibitors (ACE-Is) are used as antihypertensive medications. Arterial hypertension seems to be associated with immune (CD8 and T lymphocyte) dysfunction that may lead to a reduced ability to fight viral infections and to a cytokines dys-regulation that may have contributed to the systemic inflammatory respiratory syndrome (SIRS) and acute respiratory distress syndrome (ARDS). ACE2 down-regulation is reported also in patients with diabetes mellitus as well as increased pro-inflammatory cytokine expression which can contribute to the cytokine storm and uncontrolled inflammation in the lungs in patients with the COVID-19 (Gold et al. 2020). Increased ACE2 expression in patients with cardiovascular diseases could lead to direct infection of cardiovascular tissue and subsequent the common and fatal manifestations of COVID-19 such as myocarditis (Gold et al. 2020).

COVID-19 affects many organic systems, primarily pulmonary and cardiovascular system, gastrointestinal tract, but also central and peripheral nervous system, urogenital tract, endocrine system liver, spleen, skin, blood (see table 2). The most frequent clinical manifestations are fever, dry cough, dyspnea and fatigue, while other symptoms involve headache, myalgia and arthralgia, chills, conjunctival and nasal congestion, sore throat, nausea and vomiting, diarrhea and hemoptysis. The disease severity is not predictable and usually the four severity groups are reported: 1. Asymptomatic patients or patients with mild symptoms and course (mild upper or genitourinary symptoms); 2. Stable patients with respiratory symptoms and radiological pneumonia; 3. Unstable patients with respiratory failure; 4. ARDS patients with multi-organ failure, impaired consciousness, shock, sepsis and death (see Kotfis et al. 2021). It is important to have in mind that many patients who recovered from COVID-19 still have systemic symptoms related to different organs, even if they do not have harbor SARS-CoV-2 by PCR testing (Li et al. 2021).

SARS-CoV-2 induces endothelial damage, thrombo-inflammation, dysregulation of immune responses, and maladaptation of ACE-2 related pathways. ACE-2, the entry receptor for SARS-CoV-2 is expressed in multiple tissues: vascular endothelia, cardio- and cerebrovascular systems, lung, kidney, small intestine epithelial cells, and testis (Atlante et al. 2020). The ACE-2 receptors have pleitropic roles in the stress response and mood regulation (Debnath et al. 2020). COVID-19 symptoms may start as mild and become intensified over 5-7 days,

Table 2. Multisystem manifestations of COVID-19 (Romagnolo et al. 2020, Tabary et al. 2020, Gavriatopoulou et al. 2020, Steardo et al. 2020, Palanti et al. 2020, Lai et al. 2020, Yachou et al. 2020, Galanopoulos et al. 2020, Sinanovic et al. 2020)

Pulmonary manifestations (81% PulmoCOVOD-19): alveolar epithelial cells; alveolar injury and interstitial inflammation; immune system activation, pro-inflammatory factors, cytokine storm; diffuse pulmonary intravascular coagulopathy; silent hypoxia and atypical ARDS.

Cardiovascular manifestations (8.9-52% CardioCOVID-19): acute myocardial infarction, myocarditis, decompensated heart failure, arrhythmias; generalized endothelial dysfunction; Kawasaki-like syndrome, blood clots; pulmonary, coronary, cerebral or peripheral thromboembolism, cardiomyopathy, acute cor pulmonale, cardiogenic shock, sudden cardiac death.

Nervous system manifestations (40-88% NeuroCOVID-19): direct CNS invasion, hematogenous dissemination, or via the retrograde neuronal route, eg. olfactory neurons; hyperinflammatory status with cytokine-mediated brain damage; host immune response effects; cerebrovascular disease on the ground of hypercoagulation; headache (13.1%), dizziness (16.8%), myalgia, fatigue, anorexia, anosmia or hyposmia (86%), ageusia (88%), acute stroke, confusion or impaired consciousness, Guillain-Barre syndrome, meningitis and encephalitis, hemorrhagic posterior reversible encephalopathy syndrome, acute necrotizing encephalopathy.

Mental manifestations (PsychoCOVID-19): may result from systemic inflammation or direct virus penetration into brain, and from distress due to experience of potentially lethal and untreatable COVID-19. Mental disorders may appear due to CNS effects of cytokines, neuroinflammation, glial dysfunction or aberrant epigenetic modifications of stress-related genes.

Hematologic manifestations: infection of lymphocytes, cytokine-induced lymphocyte apoptosis; endothelial dysfunction and immune dysregulation, and blood hypercoagulability; systemic inflammation and increased inflammatory parameter: lymphopaenia (56.5-80%), leukocytosis (neutrophylia), thrombocytopenia (16.4-32.3%), increased neutrophil-lymphocyte ratio (80%), thrombotic processes.

Renal manifestations (0.5-23%): uncontrolled systemic inflammatory response, and acute kidney injury: electrolyte abnormalities (hyperkalemia, hyponatremia or hypernatremia), metabolic acidosis, haematuria (26.7%), proteinuria (43.9%)

Gastrointestinal manifestations (12-61% GastroCOVID-19): direct infection and apoptosis of the epithelial cells in GI tract; gut dysbiosis: anorexia (39-9-83.8%), nausea and or vomiting in 7%, diarrhea (9-50%), abdominal pain in 3%.

Hepatic and billiary manifestations (16.1-53.1%): abnormal aspartate or alanine transferase values, direct infection and apoptosis of hepatocytes, hypoxia, sepsis.

Endocrine manifestations: molecular mimics to the host ACTH, cortisol insufficiency; direct infection, degeneration and necrosis of the adrenal gland; ACE2 expressed on hypothalamic and pituitary issues, direct hypothalamic damage and hypophysitis; worsened hyperglycemia, euglycemic ketosis, classic diabetic ketoacidosis.

Ophtalmologic manifestations (1.1-15.9%): conjunctival congestion alone, conjunctivitis, retinal changes.

Cutaneous manifestations (1.1-20%): direct virus infection, related to underlying vasculopathy, secondary to host immune response: erythematous rash, urticaria, chicken pox-like vesicles.

Reproductive system manifestations: testicular pain, orchitis.

and if pneumonia develops may worsen severely, sometimes requiring intubation and mechanical ventilation. Some infected individuals do not develop any symptoms at all. Clinical manifestations and outcomes are related to the age, sex, ACE2 expression and comorbidities (see table 3). Individuals with underlying diseases such as arterial hypertension, diabetes, lung, liver and kidney diseases, cancer, as well as patients on chemotherapy or taking steroids chronically are at increased risk of SARS-CoV-2 infection and developing severe forms of the COVID-19 (Sanyaolu et al. 2020). Chronic non-communicable diseases may be linked to the pathogenesis of COVID-19 because they share several pathological mechanisms with infectious diseases, such as the inflammation, and the decreased innate immune response. According to the concept of the gut-lung axis crosstalk a gut microbial imbalance can affect the lungs, and vice versa an inflammation in the lungs can affect the gut's microbiome (Fakhroo et al. 2021). Comorbidities increase the chances of infection, severity of disease progression and risk of death (see table 4), not only in elderly person. It is interesting that aspirin may interfere with replication of different corona-viruses and so decrease their titers (Gold et al. 2020).

Concept of syndemics was developed in the early 1990s by Meryl Singer and colleagues on the observation that communities most affected by a new epidemic commonly were already facing other health problems, usually in the form of epidemic (see Singer & Snipes 1992, Singer 1996, Singer, Bulled & Ostrach 2020). Syndemic concept integrates two phenomena: disease or epidemic co-occurrence and disease or epidemic interaction.

Table 3. Comorbidities, symptoms, and targets concerning SARS-CoV-2 (Ejaz et al. 2020, Romagnolo et al. 2020)

Disease	SARS CoV2 targets	Symptoms
COPD	Upregulate ACE2 expression	Severe hypoxemia, hypermucous production, microbiome imbalance
Asthma	Delayed innate antiviral immune response and delayed secretion of interferon (IFN) delta	Chronic respiratory diseases along with pneumonia-like symptoms
Malignancy	Impaired immune system	Adult respiratory distress system
Obesity	The abnormal secretions of cytokines, adipokines, and interferons	Chronic low-grade inflammation of abdominal obesity with effect on bronchi and lung parenchima
Diabetes	ACE-2 expression, impaired T-cell function & increased IL-6	Pneumonia-like symptoms
Hypertension	Upregulate ACE-2 expression	Increased blood pressure with pneumonia
Cardiovascular diseases	Impaired immune system Diseases ACE2 expression	Myocardial injury, heart attack
Brain diseases	Impaired immune system damage of respiratory center	Cerebrovascular disease, cognitive impairment
Liver diseases	ACE-2 expression in liver cells	Elevated serum aminotransferases
Renal diseases	Increase secretion of dipeptydil peptidase-4 and ACE-2	Acute kidney injury

Table 4. Comorbidities among COVID-19 deaths (Sanyaolu et al. 2020, Ejaz et al. 2020, Gelburd 2020)

Comorbidities	Death %			
	Sanyaoly et al.	O'Brien at al.	Harrison et al.	Ejaz et al.
Arterial hypertension	55.4%	15%		9.5-73.8%
Diabetes	37.3%	12%	32.4%	7.4-58%
Hyperlipidemia	18.5%			
Coronary artery disease	12.4%			
Ischemic heart disease		13%		
Myocardial infarction			20.2%	
Renal disease	11.0%		37.5%	0-7-21%
Dementia	9.1%	42%w - 33%m	15.4%	
COPD	8.3%			7-3-42.5%
Chronic pulmonary disease			30.2%	
Cancer	8.1%	8%		
Any malignancy			14.8%	2-9-5%
Atrial fibrillations	7.1%			
Heart failure	7.1%			
Congestive heart failure				30.8%
Cerebrovascular disease				19.6%
Liver disease			9.3%	0-6-3.7%
Patients with comorbidities (Gelburd 2020)	83.29%			

Concept of syndemics refers to the interaction of multiple epidemics that significantly worsen the outcome of disease in certain populations and increase health vulnerability. Individuals with underlying health conditions and the elderly, but also the all those whose immune systems are weaker, are substantially more at risk from SARS-CoV-2 (Irons 2020). In other words when two or more epidemics occur together and influence one another to worsen disease outcome, they are defined to be syndemic or synergistic epidemics. The term syndemic has usually been used to describe disease clusters at the individual level (Kenny 2020). The concept of syndemics helps us to understand how epidemics interact at the both levels: the level of populations and the level of individuals and enable appropriate interventions (Tsai et al. 2017).

Syndemics of COVID-19 play an important role in shaping disease outcome. Syndemics theory provides a conceptual model for research and understanding of the ways biological, psychological, social, economic and political conditions promote mechanisms of adverse synergistic COVID-19 interactions. The concept of COVID-19

syndemics involves multiple dimensions of analysis: disease concentration, disease interaction, and the large scale of psycho-social and infodemic forces that enhance negative consequences. The dimension of disease concentration refers to appearance of two or more epidemics that co-occur in particular temporal or geographical context due to harmful social, political, economic, and cultural factors (see Tsai et al. 2017). The dimension of disease interaction refers to synergism and increasing deleterious consequences for health and life both at the level of populations and the level of individual consequences. The prevalence of NCDs has increased dramatically over the past several decades, particularly in low- and middle-income countries characterized with the highest mortality rates from these diseases (Herrick 2020). Obesity, a risk factor for COVID-19 because it causes a low grade chronic inflammation, affects the immune system, gut microbiome-virome balance, and antiviral response is a global epidemic (Fakhroo et al. 2021). Diabetes which is prevalent in COVID-19 patients is one of the fastest growing diseases in modern world. Obesity, diabetes and cardiovascular disorders are associated with "gut dysbiosis" which may partly explain COVID-19 severe clinical outcomes.

ATTEMPTS TO TREAT COVID-19

There are still no officially approved therapeutic drugs for COVID-19 (the compilation of literature is presented on table 5), but several vaccine types entered the clinical practice. Effective and safe vaccines are the ultimate measures to reduce COVID-19 morbidity and mortality rates. S protein is recognized as a strategic key for vaccines and novel anti-SARS-Cov-2 drugs. Remdesivir, a nucleotid analog that inhibits viral RNA polymerases and lopinavir-ritonavir, a human immunodeficiency virus (HIV) medication have shown inhibitory activity against SARS-CoV-2 (Gosain et al. 2020). Immunomodulators decrease the pulmonary inflammatory response (the so called "cytokine storm") and improve the alveolar-capillary gas exchange improving oxygenation and enabling survival (Gosain et al. 2020). Glucocorticoids are believed to prolong the viral shedding time and maintain a systemic anti-inflammatory state decreasing ARDS. The antibodies in convalescent plasma obtained from patients who have previously recovered from the COVID-19 are reported to neutralize SARS-CoV-2 and limit its replication (Gosain et al. 2020).

Table 5. Treatment attempts of SARS-CoV-2 (Gosain et al. 2020, Singh 2020, Atlante et al. 2020, Fakhroo et al. 2021, Kotfis et al. 2021)

Antiviral drugs: Remdesivir, Lopinavir-ritonavir
Immunomodulators: Cytokine inhibitors: IL-6 inhibitors (tocilizumab, sarilumab, colchicine), Janus kinase (JAK) inhibitors (baricitinib, fedratinib, ruxolinitinib), Spingosine-1-phosphate receptor (SiPR1) agonist (fingolimod), Specific TNF blockers (infliximab, adalimumab), Serin-protease inhibitors (gabexate), Anti-GM-CSF, Bruton tyrosine kinase inhibitor Mesenchymal stem cells, Glucocorticoids; S1R agonists (fluvoxamine)
Convalescent plasma
Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors: angiotensin II receptor blocker: Losartan (antihypertensive drug)
Mineralocorticoid receptor antagonists and androgen inhibitor: Spironlactone, Potassium canrenoate (anti-hypertensive and antiandrogenic medication)
Extracorporeal Membrane Oxygenation (ECMO)
Tissue plasminogen activator (tPA)
Low molecular weight heparin (LMWH):
Vitamins: vitamin D, vitamins B9 and B12, vitamin A, vitamin C, vitamin E
Probiotics and prebiotics
Traditional Chinese medicine: Qingfei paidu
Phytochemicals and natural products: Flavonoids (luteolin, myricetin, quercetin, apigenin)
Epigenetic modulators:
- *DNA methyltranspherase inhibitors (DNMTi)*- Azacitidine, Decitabine, Curcumin;
- *Histone deacetylases inhibitors (HDACi)* - Vorinostat or suberanilohydroxamic acid (SAHA), Valproic acid (VPA), Panobinostat;
- *Histone methyltransferases inhibitors (HKMTi*): Cheatocin, DZNep;
- *Histone acetyltransferase inhibitors (HATi):* Anacardic acid, MG149
- Locked nucleic acid antisense oligonucleotides (LNA): Miravirsen

Table 6. Potential mechanisms of fluvoxamine action in COVID-19 patients

Anti-inflammatory and immunomodulatory mechanisms: Fluvoxamine, SSRI and S1Rs agonist, reduces the production of interleukins(ILs): IL-6, Il-1beta,IL-8 and IL-12 decreasing possibility for hypercytokinemia and cytokine storm. It inhibits cyclooxygenase 2 expression what decreases production of prostaglandine E2 and consequently decreases IL-6 and inflammation.
Anticoagulant mechanisms: Fluvoxamine and other SSRIs reduce serotonin concentration in platelets decreasing possibility of hypercoagulation.
Lysosomotropic mechanisms: Fluvoxamine can passively diffuse through the endosomal membrane and become protonated and trapped in an acid PH milieu of the vesicles and by changing the intravesical pH level may interrupt SARS-CoV-2 fusion and dissemination.

Autoantibodies present in autoimmune diseases can also be detected in COVID-19 patients and some medications used to treat autoimmune rheumatologic disease are reported to may have therapeutic effect in COVID-19 (Liu et al. 2021). Extracorporeal membrane oxygenation (ECMO) may be a life-saving treatment method for the most severe COVID-19 patients with refractory respiratory failure. Tissue plasminogen activator (tPA) intravenously may help in critically ill, mechanically ventilated COVID-19 patients with ARDS and concomitant DIC (Gosain et al. 2020). Low molecular weight heparin (LMWH) decreasing the levels and biological activity of IL-6 may reduce mortality of COVID-19 patients with sepsis-induced coagulopathy (Gosain et al. 2020). Spironolactones, drugs approved for the treatment of heart failure with reduced ejection fraction, refractory hypertension, primary hyperaldosteronism, and oedema secondary to cirrhosis or nephronic syndrome, are suggested to be able to prevent acute lung due to its pleiotropic effects with RAAS and ACE2 expression, reduction in TMPRSS2 activity and antiandrogenic action (Kotfis et al. 2021). The common inflammatory-mediated mechanism of COVID-19 and autoimmune diseases open the possibility of positive therapeutic effects of immunomodulators (see table 5). The outpatients with COVID-19 treated with fluvoxamine (SSRI with agonistic effect on sigma-1 receptors (S1R) compared with placebo had a lower likelihood of clinical deterioration over 15 days (Lenze et al. 2020). Explanation of the potential fluvoxamine benefit in patients with COVID-19 (see table 6) involve its influence on S1R-IRE1 pathway with cytokine reduction, direct antiviral effects via its lysosomotropic properties, modulation of IRE1 effect on autophagy and SSRI inhibition of platelet activation (Lenze et al. 2020). There is an interesting report about melatonin associated with more frequent survival of intubated COVID-19 patients (Ramlall et al. 2020).

Treatment for COVID-19 patients suffering from comorbid NCDs should be strictly personalized. The epigenomic research of specific epigenetic mechanisms might open new paths for more precise and specific epigenetically based therapies (see table 6). Both systemic treatments and organ specific treatment strategies are required to overcome COVID-19.

Vitamin D is reported to have essential role in immunomodulation, lung and muscle function, cardiovascular health, and infectious disease prevention (Xu et al. 2020). It could reduce apoptosis of pneumocytes and stimulate surfactant to prevent severe lung damages such as ARDS (Xu et al. 2020). Vitamin D might aid in preventing COVID-19 through immunomodulation, while stimulating expression of neurotrophins such as Nerve Growth Factor (NGF) might prevent loss of neural sensation (Xu et al. 2020).

EPIGENETICS OF COMORBIDITY AND SYNDEMICS OF COVID-19

> *„Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals respond alike and behave alike under the abnormal conditions which we know as disease“*
>
> *William Osler*

Epigenetics, “the new science of self-empowerment” according to Lipton (2008), suggests a novel approach to understanding, prevention and treatment in the personalized or precise medicine of the 21st century, but the field is still in its infancy (Jakovljevic & Ostojic 2013). It has been considered crucial for understanding the pathophysiology of comorbidity, syndemics and infectious disease. Epigenetics studies stably heritable phenotype resulting from changes in chromatin structural/activation states without changing the DNA primary nucleotide sequence, while epigenomics studies epigenetic mechanisms which are reversible, flexible, and quickly responsive to environmental changes and stresses and which control entire genome at various levels (see Atlante et al. 2020). Today it is possible to create high-resolution epigenome maps of healthy and diseased cells with simultaneous analysis of genetic and epigenetic changes (Atlante et al. 2020). Epigenetic regulation promotes changes in the function of the gene locus without changing the sequence of the underlying DNA (Elrashdy et al. 2020). The concept of epigenetic changes has added a new dimension to the study and our understanding of comorbidity and multimorbidity as well as of variability in disease course. It seems that epigenetic mechanisms have an essential role in the development of many common disorders and illnesses,

particularly of age-related diseases. There are three basic molecular epigenetic mechanisms: DNA methylation, histone modification and microRNA dysregulation. DNA methylation, associated with suppression of gene transcription, and histone modification by acetylation, methylation, phosphorylation, and ubiquitylation have a powerful control over the activation or repression of the associated genes (Sweat 2009, Hsieh & Eisch 2010). Viruses are able to influence the host epigenome via a set of highly evolved, intricate, and well-coordinated processes promoting the robust virus replication and pathogenesis (see Elrashdy et al. 2020).

COVID-19 is a multisystemic disease characterized by heterogeneous clinical manifestations, ranging from mild flu-like symptoms to multiple organ systems failure and deadly acute respiratory distress syndrome with different comorbid diseases. COVID-19 severity and consequences depend on patient age and previous comorbid diseases. The higher prevalence of severe COVID-19 in patients with pre-existing diseases and disorders is related to their intrinsic epigenetic fragility and decreased resilience and ability to compensate for COVID-19. A hypothesis on SARS-CoV-2 epigenetic remodeling of host cell metabolism is very interesting and different epigenetic mechanisms may play a key role in the onset and severity of symptoms and complications in COVID-19. DNA methylation variability of the ACE2 gene and post-translational changes in histones could explain differences observed during COVID-19 related to biological age and sex patterns (see Freitas et al. 2020, Ragia & Manolopoulos 2020). SARS-CoV-2 utilizes different epigenetic mechanisms to inhibit initiation of the host innate immune response. It initiates cytokine storm and induces various cell death programs like pyroptosis, apoptosis, and necrosis which may be important part of COVID-19 pathology (Elrashdy et al. 2020). In patients with systemic lupus erythematosus with elevated ACE2 levels due to the hypomethylation and overexpression of ACE2, SARS-CoV-2 induces oxidative stress causing exacerbation of these lupus-related DNA methylation affections and causes further ACE2 hypomethylation accompanied by the overexpression of ACE2 and increased viremia (Elrashdy et al. 2020). The more effective approaches for COVID-19 prevention and treatment are predicated on better understanding of different molecular mechanisms associated with epigenetic control (see table 3) involving the regulation of the host immune response.

COVID-19 infodemic, empathy and epigenetics of health

Cultural and psychosocial determinants of communication, health and disease have important role in the COVID-19 triad. Due to general impossibility to control the accuracy and authenticity of the majority of information in public circulation, COVID-19 infodemic with massive frequency of fake news, pessimistic reports, misinformation, conspiracy theories and blame games has increased negative emotions and inappropriate behavior causing significant harm in terms of psychosocial implications and public mental health (Jakovljevic et al. 2020). It has deleterious consequences for the mental health such as health anxiety, irritability, phobia, panic reactions, depression, obsession and even COVID-19-related psychosis (see Pedrosa et al. 2020). It is well known that infodemic may negatively alter risk perceptions, encourage destructive behaviors and support the non-compliance with safe measures such as physical distancing, work from home, etc.

Strategies that may empower society and positively influence on pandemic-related stress involve 1. assessment of the accuracy of information in infodemics to prevent health anxiety and destructive behavior; 2. enhancement of a culture of trust, empathy and social support which are essential for tension release and emotional catharsis; 3. the reduction of stigma associated with COVID-19; 4. adherence to safety measures and maintaining life as normally as feasible; 5. expressing and enhancing general solidarity including that supported by psychosocial and spiritual services (Rajkumar 2020).

COVID-19 HEALTH CRISIS AND MORE HOLISTIC, PRECISE AND PERSON-CENTERED MEDICINE

Fighting the dark COVID-19 triad contemporary medicine and psychiatry face a challenge and an opportunity: the challenge of addressing multidimensional crisis and failures and the opportunity for implementing a more precise and person-centered medicine. Contemporary medicine due to technological progress is already in the process of changing its paradigms towards the introduction of a precise, personalized and person-centered medicine (see Jakovljevic & Jakovljevic 2019). The scientific community is currently trying to understand host-SARS-CoV-2 interactions and to develop effective treatments. Genetic and epigenetic polymorphism of ACE2, TMPRSS2 and FURIN genes as essential factors for SARS-CoV-2 cell entry as well as variations in expression of CALM, ADAM-17, AR and ESRs may distinguish individuals with increased risk for SARS-CoV-2 infection from those who are potentially resistant (Ragia & Monolopoulos 2020). Studying the potential biological factors - in addition to psychosocial, economic and cultural factors - such as epi/genetic polymorphisms that are associated with COVID-19 susceptibility, morbidity and mortality is fundamental for recognizing disease risk and establishing novel precise, personalized treatment options (Li et al. 2021). Epigenome mapping, together with epigenome-wide associaion

studies (EWAS) and genome-wide association studies (GWAS) could improve individual diagnostics and personalized therapies. COVID-19 crisis is an opportunity for humankind to promote antifragility through a global hero's journey towards compassionate society and empathic civilization (see Taleb 2013, Jakovljevic et al. 2020). In the same light and spirit it is an opportunity for promoting more holistic, precise, personalized and person-centered medicine. Integrated network analysis and biomedical data integration (e.g. United Knowledge Space) may help to elucidate the molecular alterations specific for SARS-CoV-2 infection (Pavel et al. 2021). The issue of COVID-19 as multi-system disease and CNCDs as risk factors for COVID-19 highlights the intricacy and importance of integrative systems medicine and the complexity of providing transdisciplinary holistic understanding and health care.

CONCLUSIONS

COVID-19 syndemic and infodemic are rcognized as a great challenge to medicine, society and humanity in general. The higher prevalence of severe COVID-19 in patients with pre-existing diseases and disorders is related to their intrinsic epigenetic fragility and decreased resilience and low ability to compensate for COVID-19. The COVID-19 dark triad is not only a unique test for our basic understanding of individual, public and global health, comorbidities and multisystem diseases but also it stress a need for trans-disciplinary integrative approach and bringing separated branches of medicine to closer cooperation. All the major branches of medicine have to be pulled together if they are to work seamlessly in this time of great challenges.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Miro Jakovljevic: concept and design of article, literature searches, writing manuscript, approval of final version.

Miroslav Samarzija: added some useful ideas to concept and design of article, correction of manuscript, approval of final version

Davor Milicic: added some useful ideas to concept and design of article, correction of manuscript, approval of final version

Zeljko Reiner: added some useful ideas to concept and design of article, correction of manuscript, approval of final version

Norman Sartorius: added some useful ideas to concept and design of article, correction of manuscript, approval of final version

The article is result of the long term authors' cooperation in the field of medicine of comorbidity.

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