

**THE CROATIAN ACADEMY OF SCIENCES AND ARTS**  
**The Department of Biomedical Sciences in Rijeka**  
**UNIVERSITY OF RIJEKA**  
**THE CLINICAL HOSPITAL CENTER RIJEKA**  
**UNIVERSITY OF RIJEKA - MEDICAL FACULTY**  
**UNIVERSITY OF RIJEKA - FACULTY OF HEALTH STUDIES**  
**THE CROATIAN MEDICAL ASSOCIATION – Branch office Rijeka**

**48<sup>th</sup> Symposium**

**POST – COVID ERA: THE NEW AND  
UNKNOWN FIELD**



**KBCri**

**Rijeka, April 7- 8, 2021**  
**University Campus Rijeka, Faculty of Civil Engineering**  
**Lecture hall G-003, Radmile Matejčić 3, Rijeka**

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**Registration: online via [registration form](#) for online and onsite participants**

**Event address for ZOOM attendees will be sent to all registered participants  
by e-mail**

Free admission for both registrations, but note that the capacity of the lecture hall is restricted. Once all spaces have been filled, no more onsite registrations will be permitted. Participants who want a certificate from the Croatian Medical Chamber need to register.

### ***Information***

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# PROGRAM

1<sup>st</sup> day – April 07<sup>th</sup>, 2021

**OPENING**  
**(15,00 – 15,15)**

## ***Introduction***

**Daniel Rukavina**, M.D., PhD, Professor Emeritus, Head of the Department of Biomedical Sciences in Rijeka, Croatian Academy of Sciences and Arts, President of the Scientific Committee

**Alen Ružić**, M.D., PhD, Professor, Medical Faculty, University of Rijeka, Head of the Clinical Hospital Center Rijeka, Rijeka, Croatia; President of the Organizing Committee

## ***Welcome address***

**Srđan Novak**, M.D., PhD, Professor, Medical Faculty, University of Rijeka, Clinical Hospital, Center Rijeka, Rijeka, Croatia, Head of the Croatian Medical Association – Branch office Rijeka

**Daniela Malnar**, M.D., PhD, Professor, Dean, Faculty of Health Studies, University of Rijeka, Rijeka, Croatia

**Goran Hauser**, M.D., PhD, Associate Professor, Dean, Medical Faculty, University of Rijeka, Rijeka, Croatia

**Snježana Prijic Samaržija**, PhD, Professor, Rector, University of Rijeka, Rijeka, Croatia

**15,15 – 19,40 h**

## **I. CURRENT KNOWLEDGE**

**Chairmen: Igor Barković and Melita Kukuljan**

**Pero Lučin**, M.D., PhD, Professor, Medical Faculty, University of Rijeka, Rijeka, Croatia

**Cell biology of viral infection and COVID - 19 antiviral drugs**

**Vanda Juranić Lisnić**, PhD, Assistant Professor, Medical Faculty, University of Rijeka, Rijeka, Croatia

**Long COVID - 19 or post-COVID - 19: the insight into pathophysiology**

**Martina Pavletić**, M.D., Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**Will health care be fundamentally changed post COVID - 19?**

**Alen Protić**, M.D., PhD, Associate Professor, University of Rijeka, Medical Faculty, Clinical Hospital Center Rijeka, Rijeka, Croatia

**COVID - 19 intensive care respiratory therapy and outcomes**

**Ljiljana Bulat Kardum**, M.D., PhD, Associate Professor, Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**Long-term Health Consequences of Covid - 19**

**Break for refreshment: 17,45 - 18,00**

**Igor Barković**, M.D., PhD, Assistant Professor, Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**Long term respiratory complications of COVID - 19**

**Melita Kukuljan**, M.D., PhD, Associate Professor, Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**Chest CT - imaging in post-COVID - 19 patients**

**Snježana Juričić**, univ. bacc. med. techn., Clinical Hospital Center Rijeka, Faculty of Health Studies, University of Rijeka, Rijeka, Croatia.

**Nursing management in post COVID-19 era**

**Morana Magaš**, mag. med. techn., Clinical Hospital Center Rijeka, Faculty of Health Studies, University of Rijeka, Rijeka, Croatia

**Post-COVID protocols for infection control – the new normal**

**19,40 – 20,15 h**

## **II. ROUND TABLE DISCUSSION**

**Chairman: Alen Protić**

## 2nd day – April 8th, 2021

15,15 – 18,30 h

### I. STATE OF THE ART AND CLINICAL EXPERIENCE

**Chairmen: Vladimira Vuletić and Luka Zaputović**

**Alen Ružić**, M.D., PhD, Professor, Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**Review of cardiac manifestations and predictors of outcome in COVID - 19**

**Luka Zaputović**, M.D., PhD, Professor, Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**COVID - 19 and the cardiovascular system – special focus on thromboembolic events**

**Nenad Bogdanović**, M.D., PhD, Professor, Department for Neurobiology, Caring Science and Society, Division of Clinical Geriatrics, Karolinska Institute, Stockholm, Sweden

**Cognitive problems and post-COVID - 19**

**Break for refreshment: 16,45 - 17,00**

**Paolo Manganotti**, M.D., PhD, Professor, Department of Neurology, University Hospital Cattinara, Trieste, Italy

**Peripheral neurological symptoms and post-COVID - 19**

**Zdravka Poljaković**, M.D., PhD, Professor, Medical Faculty, University of Zagreb, Zagreb, Croatia

**Cerebrovascular symptoms and post-COVID - 19**

**Vladimira Vuletić**, M.D., PhD, Assistant Professor, Medical Faculty, University of Rijeka, Clinical Hospital Center Rijeka, Rijeka, Croatia

**Movement Disorders and post-COVID - 19 neurological syndrome**

18,30 – 19,15 h

### II. ROUND TABLE DISCUSSION

**Chairman: Nenad Bogdanović**

# ABSTRACTS

## Cell biology of viral infection and COVID-19 antiviral drugs

**Pero Lučin**

Department of Physiology and Immunology, University of Rijeka  
Faculty of Medicine, Rijeka, Croatia

Viruses are intracellular pathogens that take advantage of host-cell machinery to establish infection and replication niches within infected cells. The infection establishment is associated with the passage through the plasma membrane, unpackaging of virions, and delivery of viral nucleic acid, either RNA or DNA, at the site of viral nucleic acid transcription and replication. The entry of a virus into infected cells requires the exploitation of host-cell membranous organelle machinery to overcome the physical barrier for unpackaging of viral capsid into the cytosol. Unpacked capsids release viral nucleic acid, which initiates the viral reproduction cycle either in the cytosol or in the nucleus, where a complex replication compartment is being established. For reproduction in the cytosol, viruses exploit cytosolic components of the host cell and membranous organelles to develop replication niches. For reproduction in the nucleus, viruses should shut off host-cell processes and retain some cellular processes required to establish the replication compartment. Upon replication, newly formed capsids again exploit host-cell processes for transportation to the site of final envelopment and the egress of nascent virions from the infected cell to ensure the spread of infection. Thus, both cytoplasmic and nuclear replicating viruses interfere and exploit host cell machinery, including a considerable number of host-cell components organized into networks that execute complex integrated functions. For example, just for entry and final envelopment processes, viruses can potentially interfere with products of more than three thousand cellular genes. Thus, understanding the cell biology of these interactions is a huge task and requires understanding the host-cell cellular physiology to identify potential targets that can be exploited by products of virus-encoded genes. Consequently, understanding virus-host cell interactions is a prerequisite for identifying potential targets for antiviral interventions, including the development of antiviral drugs and antiviral therapies.

This presentation will focus on the cell biology of the SARS-CoV-2 virus, a relatively small RNA virus that replicates in the cytoplasm, and cytomegalovirus (CMV), one of the largest viruses that replicate in the nucleus and establish the most complex interactions with host-cell physiological networks. The basic organization of the SARS-CoV-2 and CMV replication cycle will be presented with the particular focus on the utilization of membranous-organelle machinery for the establishment of infection, development of the replication niches, final envelopment of the nascent virions, and virion egress for the spread of infection. In addition to the classical cell biology approaches, the particular focus will be on the systemic approaches in understanding membranous organelle utilization and host-cell remodeling, including recent spatial proteomics and recycle-ome studies. Accordingly, the potential sites and efforts of antiviral interventions using small-molecule antiviral drugs will be discussed.



**Keywords:** cellular physiology of virus infection, SARS-CoV-2 virus, cytomegalovirus, the membranous system of the cell, virus replication, antiviral drugs

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## **Long COVID-19 or post-COVID-19: the insight into pathophysiology**

**Vanda Juranić Lisnić**

University of Rijeka, Faculty of Medicine, Center for proteomics  
and Department for histology and embryology, Rijeka, Croatia

Infectious diseases pose the greatest threat to public health than any other diseases or syndromes. The current COVID-19 pandemic has underscored not only this fact but also highlighted the difficulties in managing world-wide pandemics. Nevertheless, this pandemic has also instigated unprecedented world-wide scientific response and effort to bring novel vaccines with previously unimaginable speed. Although the mortality from COVID-19 is not very high, the sheer number of cases resulted in very high number of excess deaths. According to the World Health Organization, as of early March 2021 there are over 116 million of confirmed COVID-19 cases worldwide with over 2.6 million deaths. Likewise, while long-term consequences such as fatigue, respiratory, heart and neurological problems (termed long COVID-19) currently seem to affect one in ten infected individuals, the number of affected patients worldwide will be significant and will require interdisciplinary preclinical and clinical approaches to determine causes and provide management options. Preexisting knowledge based on related corona viruses, especially SARS CoV, has so far proven very useful both in vaccine design and pandemics management. When it comes to long-COVID, chronic fatigue syndrome has been reported in 40% had chronic fatigue and over 20% have been diagnosed.

## **Will health care be fundamentally changed post COVID-19?**

**Martina Pavletić**

Emergency Department, Clinical Hospital Center Rijeka, Rijeka, Croatia

The main focus is in which direction health care will change and how deeply. The COVID-19 pandemic has changed almost every aspect of our lives, and health care has not been ruled out. The new normal is marked as something inferior and different from the old or “known normal”. In healthcare, from a hospital perspective, we have been faced with many obstacles in how to adapt our established way of thinking and knowledge to the new situation and the new demands placed on us by the pandemic. Once again, nature has shown us that humanity is small, and sometimes incompetent and unprotected despite the great advances of technology and science back several decades. The warning of nature has been strong and thorough, and the consequences cannot yet be fully seen and predicted in the economy, education, other public aspects of human action, or in the health system. One of the main and open issues is health, especially the mental health of healthcare workers who are committed to risk for more than a year working to provide their patients with the necessary healthcare. The COVID-19 pandemic has undoubtedly brought a number of very negative impacts to the

health system, but at the same time it has improved many things with great advances in organizations and management. One of the best “products” was better communication and connection between different areas of medicine and the health system itself, and between basic science and clinical medicine - translation medicine, as we call it. We hope that the good clinical practice and improvements that result from this pandemic will permanently change our way of thinking and be implemented in our changed healthcare system.

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## **COVID-19 intensive care respiratory therapy and outcomes**

**Alen Protic<sup>1,2</sup>**

<sup>1</sup>Clinical Hospital Center Rijeka, Rijeka, Croatia

<sup>2</sup>Faculty of Medicine, University of Rijeka, Rijeka, Croatia

The virus is classified in the Severe acute respiratory syndrome – related coronavirus species and has been assigned the name SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), similar to those seen in previous pandemics. The clinical virus is presented from very mild symptoms of a mild cold to pneumonia, which can lead to acute respiratory failure and at a later stage of multiorgan failure with mortality of 2 to 10% which include only symptomatic Covid 19 patients. In hospitalized patients, interstitial pneumonia and ARDS usually occur during the second week of treatment, 7-9 days from the onset of the first symptoms. Non-invasive ventilation support has not been shown to be effective in treating this type of ARDS with the existing additional risk of increased disease spread to medical staff (open ventilation system). But, delaying invasive ventilation support often leads to worsening of the patient's condition. Patients with saturation of 75-80% and PaO<sub>2</sub>/FiO<sub>2</sub><150 require invasive ventilation treatment. Fulminant cardiomyopathy may occur in these patients even in the stage of recovery from the disease. It is not yet clear whether the infections cause viral cardiomyopathy or whether cardiac dysfunction is due to cytokine storm.

In theory, frequent dry cough, straining of the auxiliary respiratory muscles, poor sleep and physical exhaustion are many time the cause of respiratory insufficiency. Mechanical ventilation in this case very effectively bridges patient crises.



Early weaning from mechanical ventilation is one of the key part of successful treatment of Covid-19 patients because respiratory support in general was borderline indicated in most cases. Prolonged ventilation of patients for more than 5 – 7 days creates conditions for the colonization of other pathogens, often resistant bacteria and fungi that encounter a markedly weakened immune response of the host, which significantly shortens and accelerates the path to sepsis. For such a treatment strategy, analgesia with short-acting sedatives or anesthetics is necessary so as not to lose 1 to 3 days on the metabolism of long-acting sedatives.

Good organization of intensive care units with clearly defined protocols is important for the control and successful treatment of the most severe Covid 19 respiratory infections. Such a unit must employ a sufficient number of medical staff, primarily the most experienced intensive care physicians, medical technicians who are the most important staff (it is necessary to have a minimum of 0.75 nurses per patient), and physiotherapists whose role is important immediately after separating patients from mechanical ventilation. Sufficient quantities of quality protective equipment are a prerequisite for working with such patients, given that the families of medical staff who are in direct contact with Covid 19 patients are the most vulnerable population.

### **Long-term health Consequences of Covid - 19**

**Ljiljana Bulat Kardum<sup>1,2</sup>**

<sup>1</sup>Clinical Hospital Center Rijeka, Rijeka, Croatia

<sup>2</sup>Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Because COVID-19 is a new disease, much about the clinical course of disease remains insecure such as the possible long-term health consequences. More recently, data have emerged that some patients continue to experience symptoms related to COVID-19 after the acute phase of disease. Reports of long-lasting coronavirus COVID -19 disease symptoms are rising but little is known about prevalence, risk factors, natural history and etiology of these symptoms or whether it is possible to predict a protracted course early in the disease. Besides, there is currently no achieved consensus definition for this condition: terminology has included “long COVID,” “post-COVID syndrome” “post-acute COVID-19 syndrome” and „chronic COVID-19“. Among the lay public, the phrase “long haulers” is also being used. The syndrome appears to affect those with mild as well as moderate to severe disease.

Most studies have focused on symptoms duration and clinical outcomes in adults hospitalized with severe COVID-19. Prolonged illness is well described in patients after they have been discharged from the hospital, especially among older adults. Most of them at three months after discharge had persistent symptoms, diminished respiratory muscle strength, abnormalities in pulmonary function including decreased diffusion capacity for carbonmonoxide, and radiologic abnormalities consistent with pulmonary dysfunction such as interstitial thickening and evidence of fibrosis. Limited data are available on the course of COVID-19 symptoms in non-hospitalised patients, who constitute the majority of patients. COVID-19 can result in prolonged illness even among persons with milder outpatient illness, including young adults. It might take weeks for resolution of symptoms and return to baseline health. Most commonly symptoms reported are cough, shortness of breath, low grade fever and fatigue, all of which may relapse and remit. Other common symptoms include joint and chest pain. In addition

to these general symptoms, specific organ dysfunction has been reported, involving primarily the heart, lungs, and brain. Based on the UK COVID Symptom Study approximately 10% of people experience prolonged illness after COVID-19. This percentage is lower than that reported in many published observational studies. According to the results of one recent published US study only 65% of patients after COVID-19 infection had returned to their previous level of health 14-21 days after. It is not known why some people's recovery is prolonged. The association of persistent symptoms with comorbidities and symptom load during the acute phase of COVID-19, but not with age, was assumed. Persistent viraemia due to weak or absent antibody response, relapse or reinfection of disease, inflammatory and other immune reactions, deconditioning and mental factors such as post-traumatic stress may all contribute to development of post-COVID-syndrome. Pathophysiological parallels could be found in the past pandemics caused by other coronavirus pathogens such as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS). They have had a similar course of disease with long term respiratory, musculoskeletal, and neuropsychiatric sequelae that could linger for months in "recovered" patients.

Better understanding of convalescence and symptom duration among outpatients with post-COVID-19 can help direct care, inform interventions to reduce transmission, and tailor public health messaging. Probably, it is still early in the COVID-19 pandemic to say these, but it is possible that large numbers of patients will experience long-term sequelae. Therefore, it is imperative that the care of this vulnerable patient population take a multidisciplinary approach.

### **Long term respiratory complications of COVID-19**

**Igor Barkovic, Vuk Prica, Helena Smokrović, Christian Štemberger**  
University Hospital Center Rijeka, Rijeka, Croatia

A new virus, SARS-CoV-2, marked the whole last year and is still causing significant medical problems. Until the end of February of 2021 more than one hundred million people got infected and more than two and a half million died because of it. With such high numbers it is expected that if even a small percentage of infected people develop any long-term complications that will have a great burden on healthcare systems (1,2). KBC Rijeka formed special „Post COVID“ ward for patients with long term respiratory complications and we treated 29 inpatients and more than 350 outpatients. The virus initially infects the respiratory system, and then spreads to other organs. In its spread ACE2 receptors play a crucial role. Although many organs are involved the data suggest that the long-term effects are most pronounced in lungs. These complications include dyspnea, chronic cough, pulmonary vascular disease, fibrotic lung disease, fatigue, bronchiectasis etc. (1,2,3).

Although SARS-CoV-2 is a new virus some similarities can be seen with the outbreak of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In studies published so far it is reported that approximately 30% of patients who suffered from those two diseases had long term respiratory complications, but twelve months after the recovery only 10% of patients had parenchymal abnormalities that could be seen on a CT scan (2,4,5,6).

Other studies have investigated the long-term effects of ARDS, and patients who developed ARDS later had substantial lung fibrosis. Lung fibrosis can also be linked to

barotrauma in patients on positive pressure ventilation and oxygen toxicity for patients treated with high partial pressures of oxygen for extended time. (7,8) It is also unclear what will be the long-term implications of the initial treatment. For example, the benefit of dexamethasone in severe covid-19 has recently been established, but treatment did not improve acute outcomes among patients with milder disease (9). Pulmonary fibrosis remains a big concern in patients that had COVID-19. In these settings pulmonary rehabilitation could play a crucial role in reducing patient disability (10,11,). To conclude, although many papers have been published on the topic of COVID-19 and its long-term effects it is still not clear what the future brings. Many more studies and trials should be published.

## Literature

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## Chest CT-imaging in post-COVID-19 patients

Melita Kukuljan<sup>1,2,3</sup>

<sup>1</sup>Clinical Department for Radiology, Clinical Hospital Center Rijeka

<sup>2</sup>University of Rijeka, Faculty of Medicine, Rijeka, Croatia

<sup>3</sup>University of Rijeka, Faculty of Health Studies, Rijeka, Croatia

As the initial wave of the COVID-19 pandemic has receded, a spectrum of lung parenchymal and pulmonary vascular pathology related to acute illness has emerged. The combination of viral pneumonia and acute respiratory distress syndrome that characterises the severe manifestations of acute COVID-19 illness is considered to be a possible precursor to pulmonary fibrosis. Another major potential pulmonary morbidity is the propensity for thromboembolic phenomena, in both systemic and pulmonary circulations.

Apart from the generic risks for venous thromboembolism in acutely ill hospitalised patients, evidence is emerging for a more specific, angiocentric signature of COVID-19, related to an in-situ thrombotic microangiopathy and a complex immune inflammatory cascade, especially in the pulmonary vascular bed.

Reviews of COVID-19 CT imaging along with postmortem lung biopsies and autopsies indicate that the majority of patients with COVID-19 pulmonary involvement have secondary organising pneumonia (OP). Organizing pneumonia is a clinical entity that is associated with nonspecific clinical findings, radiographic findings, and pulmonary function test results. It corresponds to a histological pattern characterized by granulation tissue polyps within alveolar ducts and alveoli, with chronic inflammation of the adjacent lung parenchyma. Similar lesions can also be observed in the respiratory bronchioles. When the cause is unknown, OP is classified as primary or cryptogenic; when a causal connection can be established, OP is classified as secondary.

Although the diagnosis of OP is established by biopsy and histology, the clinical findings and imaging changes can suggest the diagnosis. In this context, HRCT is the imaging method of choice for diagnosing OP. In addition, HRCT allows us to evaluate the response to treatment and is useful for selecting the type of biopsy and the best site to perform it (when necessary).

The most common HRCT findings in descending order, were as follows: ground-glass opacities, consolidation, peribronchovascular opacities, reticulation, bronchiectasis, interstitial nodules, interlobular septal thickening, perilobular pattern, reversed halo sign, airspace nodules, halo sign and signs of architectural distortion. The most common finding in patients with OP is that of consolidation and ground-glass opacities, which are usually bilateral and peripheral.

OP respond very well to corticosteroid treatment; however, some patients may develop progressive fibrosis. There is a dearth of accurate data on the prevalence of pulmonary fibrosis post-COVID-19.

Delayed pulmonary embolism (PE) after COVID-19 pneumonia-many patients with proven thromboembolism in COVID-19 have been from intensive care series, but thromboembolism is now being reported in less critically ill patients in hospital and ambulatory settings.

Risk factors for thrombosis are numerous but are generally considered to contribute by three key mechanisms (Virchow's Triad); endothelial injury, reduced flow/stasis and hypercoagulable state. Although there are many unknowns with regard to this novel

disease, increasing experience suggests that patients with severe COVID-19 infection have elements of all three. Pulmonary embolism is a potentially life threatening condition requiring adequate diagnosis and treatment. Computed tomography pulmonary angiography (CTPA) is excellent for including and excluding PE, therefore CTPA is the first-choice diagnostic imaging technique in patients suspected of having acute PE. In pulmonary embolism CTPA will show filling defects within the pulmonary vasculature.

### **Nursing management in post COVID - 19 era**

**Snježana Juričić**

Clinical Hospital Center Rijeka, Rijeka, Croatia

World Health Organization declared the 2020 year of nurses and midwives, not knowing that this would be the year in which they would have the opportunity to show and prove how big their role in the health system and care for patients is. The epidemic - that is, the pandemic, SARS-CoV-2, apart from professionally has entered deep into the life of nurses privately by changing their plans and tearing down their daily lives. Reassigned to crisis workplace, education on how to use specific work protective equipment, dealing with the unknown, unpredictable working hours, caring for patients, as well as their loved ones, cessation of normal daily functioning and overall uncertainty, nurses accepted unconditionally and with enthusiasm that is only known to them. It is safe to say that nursing is experiencing a heroic age in which acceptance of responsibility, rapid adaptation to an emergency, sacrifice, love for the patient and human being is a confirmation that the profession of nurse/technician is chosen solely by the heart.

The future carries the need to adopt a new way of communicating and working with patients, a new way of cooperation with colleagues, digitalization, and the need for additional, lifelong vertical and horizontal education. It is imperative to develop specializations and expand competencies to adapt and keep pace with the challenging times partly caused and further rushed by the SARS-CoV-2 pandemic.

Experience adopt during the struggle with the pandemic is of utmost importance in preparing future events and determining the direction in the development of nursing.

### **Post-COVID protocols for infection control – the new normal**

**Morana Magaš**

Clinical Hospital Center Rijeka, Rijeka, Croatia

The SARS-CoV-2 pandemic placed many challenges in front of infection control professionals requiring an adequate response. Working at the time of the pandemic is work without precedent, and for many, it is the greatest disruptive event in professional life. In hospital condition, numerous modifications have been made in standard patient care procedures, as well as in the behaviour of employees. In the Clinical Hospital Center Rijeka with the participation of management staff of clinics, institutes, and centres, targeted protocols and work instructions were implemented. Now, in line with the easing of epidemiological measures, all protocols need to be readjusted for the post-COVID era. Lessons from the SARS-CoV-2 crisis have shown how to improve practices and how to better equip healthcare facilities for future events. Predicting what the “new normal” will look like is empowered by the experience and is less confusing.

The way of thinking has changed, the way of working with patients has changed, but also behaviour in contact with colleagues and co-workers during working hours has changed. Protocols related to patient examination, restructuring of the clinical environment, wearing personal protective equipment, maximizing the use of non-invasive techniques, and other recommendations for biological safety will certainly continue to be useful. Changing the working climate adopts behavioural patterns that are expected to be positive and effective in the prevention of hospital infections. But, only the flow of time will show if and at what point, employees and patients will return to their old habits and behavioural models.

## **Review of cardiac manifestations and predictors of outcome in COVID-19**

**Alen Ružić<sup>1,2</sup>**

<sup>1</sup>Clinical Hospital Center Rijeka, Rijeka, Croatia

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Although pulmonary manifestations are predominant in coronavirus disease (COVID-19), cardiac involvement is also very common. Manifestations of cardiovascular involvement can be very different, and in their broad spectrum, they partly overlap with the symptoms and signs of lung disease. Cardiac injury is the most common cardiovascular event and can be categorized as myocardial ischemia or non-ischemic myocardial injury. So far, multiple pathophysiological mechanisms leading to both forms of myocardial injury have been described. They are partly different but partly include common pathological processes. Strong systemic inflammation described in the literature as cytokine storm is often present in COVID-19 patients and is associated with a number of pathological conditions of the heart and blood vessels. Numerous cases of myocarditis ranging from mild left ventricular systolic dysfunction to fulminant forms presented by the dilated phenotype have been described. Strong systemic inflammation in COVID-19 patients also induces a prothrombotic state, and together they can lead to rupture of atherosclerotic plaque and induction of acute arterial occlusions, among which various forms of an acute coronary syndrome are certainly the most significant.

In COVID-19 patients, it is sometimes difficult to identify the exact mechanism of myocardial injury due to possible overlap of myocarditis, generalized hypoxic injury, cardiac microvascular dysfunction, small vessel cardiac vasculitis, endothelitis, and high risk of destabilizing atherosclerotic plaques on large coronary artery arteries. Also, the COVID-19 pandemic describes a significant number of patients who develop stress (takotsubo) cardiomyopathy during SARS-CoV-2 infection, although it is very interesting to note an increase in the number of these cardiomyopathies during pandemic in the general population, even in the group without COVID-19 infection. Pericardial effusion is common in patients with COVID-19 infection. It indicates inflammatory involvement of the pericardium, but according to the available literature is rarely of hemodynamic importance. Cases of acute cor pulmonare have also been described so far. They may be associated with pulmonary embolism which is common in these patients, but also with extensive pneumonia or respiratory distress syndrome. There is a high prevalence of ECG changes during COVID-19 infection, and these include repolarization changes, less often ST-elevation, and more often negative T-waves and ST-segment depression. Patients with COVID-19 infection also have a higher incidence of



cardiac arrhythmias than the general population. Atrial fibrillation is the most common arrhythmia in COVID-19 patients. According to the involvement of the cardiovascular system COVID-19, patients can be categorized into three basic groups: those who do not manifest clinical evidence of heart disease, some who have no symptoms of heart disease but have abnormal heart tests, and finally, those who have symptomatic heart disease have differently severe forms. Cardiac disorders are most commonly developed in COVID-19 patients with pre-existing comorbidities and high-risk profile of established cardiovascular risk factors. The prognosis of cardiovascular involvement in COVID-19 patients depends on many determinants, but in addition to age and number of comorbidities, the strongest indicators of poor prognosis are elevated serum markers of heart injury, primarily high serum troponins and natriuretic peptides, as well as the development of left ventricular systolic dysfunction.

**Key words:** cardiovascular diseases, myocardial injury, myocarditis, heart failure, pulmonary thromboembolism,

## **COVID-19 and the cardiovascular system - special focus on thromboembolic events**

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There is important bidirectional interaction between COVID-19 and cardiovascular system. Pre-existing cardiovascular diseases increase susceptibility to serious SARS-CoV-2 infection, associated with worse outcomes and higher risk of death. Although COVID-19 is primarily respiratory disease with viral pneumonia in severe cases, it can also induce cardiovascular manifestations including myocardial injury, myocarditis, heart failure, arrhythmias, acute coronary syndrome and arterial or venous thromboembolism (VTE). Risk factors for severe COVID-19 overlap with risk factors for thromboembolic events. Additionally, people who live in a nursing home or care facility, and who therefore may be less mobile, are at increased risk of both severe COVID-19 and thromboembolism. In patients with pneumonia, acute respiratory distress syndrome (ARDS) and sepsis, incidence of atrial fibrillation is high. Recent observational studies have shown that new-onset or recurrent atrial fibrillation may be triggered by COVID-19, with a subsequent risk of cardioembolic stroke. Clinical observations of increased thromboembolic events in patients with COVID-19 suggest the presence of a hypercoagulable state. The proposed mechanisms are COVID-19-associated systemic inflammation, endothelial damage, coagulation activation, hypoxaemia and immobilization, in combination with underlying comorbidities. Venous thromboembolism, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is common complication in severe COVID-19 patients. Therefore, anticoagulation with low molecular weight heparin at standard prophylactic doses should be considered for all patients admitted to the hospital with COVID-19. The diagnosis of acute PE may be difficult, because COVID-19 respiratory symptoms largely overlap with the presentation of acute PE, and may cause underdiagnosis. Even more, the specificity of D-dimer tests may be lower in patients with COVID-19 compared to other clinical settings, but it is still advised to follow diagnostic algorithms starting with pre-test probability and D-dimer testing. Every unexpected respiratory worsening, unexplained tachycardia, a

fall in blood pressure not attributable to tachyarrhythmia, hypovolaemia or sepsis, ECG changes suggestive of PE, and signs of DVT on the lower extremities, should be suspicious for PE. The diagnostic tests for PE should not be ordered routinely, but only when it is clinically suspected, with a low threshold of suspicion. When thromboembolic event is confirmed, treatment should be guided by risk stratification in accordance with the current European Society of Cardiology Guidelines. Non-vitamin K antagonist oral anticoagulants (NOACs) provide advantages over vitamin K antagonists such as warfarin, due to the lack of the need for routine monitoring and minimization of patient contact with the healthcare environment, except in some special circumstances when warfarin is indicated (prosthetic heart valves, moderate-to-severe rheumatic mitral stenosis, antiphospholipid syndrome, negative interactions of some investigational COVID-19 drugs with NOACs).

### **Cognitive problems and post-COVID-19**

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Evolving evidence indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), can cause neurological complications. Given the global dimension of the current pandemic, it is important to consider the possible long-term impact of COVID-19, potentially including neurodegenerative disorders. Since acute respiratory syndrome is the hallmark feature of severe COVID-19, most initial studies on COVID-19 have focused on its impact on the respiratory system. Previous studies demonstrating that various viruses, including in the wide CoV family, can have effects on the central nervous system thus it is a high possibility that SARS-CoV-2 infection could promote or enhance susceptibility to different forms of CNS changes that may lead to neurodegeneration as a long-term effect. The current knowledge of COVID-19 and its neurotropism is thin since it is not yet clear what is the mechanism of infection; direct or via secondary effects relating to enhanced systemic inflammatory/proinflammatory signaling. Moreover, other viral infections suggest that systemic inflammatory mediators may access the CNS and trigger damage via impaired BBB function. Systemic inflammation triggered by SARS-CoV-2 infection may further contribute to neuroinflammatory processes to promote the development of neurodegenerative disease in individuals already at risk. In addition, investigation of post-mortem brain and spinal cord tissue from deceased COVID-19 individuals (where possible) may provide evidence for parenchymal infection. The hypothesis of direct neuroinvasion of COVID-19 is based on extrapolated biological plausibility of CNS involvement where angiotensin-converting enzyme-2 (ACE-2), a potential receptor for SARS-CoV-2 entry plays an important role. ACE-2 is expressed on various brain cells and cerebral parts, i.e., subfornical organ, paraventricular nucleus, nucleus of the tractus solitarius, and rostral ventrolateral medulla, as well as in non-cardiovascular areas such as the motor cortex and nuclei raphe. The resident CNS cells like astrocytes and microglia also express ACE-2, thus highlighting the vulnerability of the nervous system to SARS-CoV-2 infection. The hematogenic pathway is an additional probable route of virus entry into the nervous system that includes the vagus nerve, the olfactory nerve, or the enteric nervous system. Furthermore, a

Th17-mediated cytokine storm is seen in COVID-19 cases with higher levels of different cytokines where some of them can cross the blood-brain barrier and activate the brain's immune cells to produce neural cytokines, leading to neuronal dysfunctions, delirium and neurodegeneration as a late long-term effect. Accordingly, the anecdotal descriptions and clinical records of serious deterioration of the clinical picture in patients with Alzheimer dementia, Parkinson disease and Lewy body dementia who survive COVID-19 infection were reported. The most common impairment reported was delirium and frequent reports of elevated inflammatory markers suggest etiology. Other studies have demonstrated that the disease involves marked increases in IL-6, TNF $\alpha$ , and IL-1 $\beta$ ; cytokines known to have a profound impact on working memory and attention. Impairment of these cognitive functions is a characteristic aspect of delirium, which suggests these cytokines as key mediators in the etiology of COVID-19 induced cognitive impairments. Researchers are encouraged to assay inflammatory markers to determine the potential role of inflammation in mediating the disturbance of cognitive function in individuals affected by COVID-19. Whether COVID-19 induces exclusively neurodegenerative forms of dementia or not is unknown and speculative. In patients who develop severe neurological complications, whenever possible, long clinical follow up and investigation of CSF samples for the presence of viral antigen/RNA and inflammatory mediators would be valuable to determine direct CNS infection. Thus, the nervous system's involvement in COVID-19 may be more than the current situation apprehends, therefore referring to the virus as an underestimated pathogen. Clinicians' and researchers' collective expertise may untie the potential of SARS-CoV-2 infection to prevent short-term and long-term CNS damage. After identifying initial neurological damages, careful monitoring of COVID-19 patients in the long term is mandatory.

**Key words:** COVID-19, SARS-CoV-2, neurodegeneration, neuroinflammation, angiotensin-converting enzyme-2, cytokines

## **Peripheral neurological symptoms and post-COVID-19**

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Since December 2019, the novel coronavirus (SARS-CoV-2) has rapidly spread worldwide, causing an increased number of hospitalization and intensive care admissions, due to severe respiratory distress. Even though respiratory symptoms play a critical role in the clinical picture, most patients with COVID-19 have also shown nonspecific neurological symptoms, such as confusion and headache, and some of them, particularly those who were characterized by a severe respiratory illness, suffered from more specific neurological manifestations, such as seizure or cerebrovascular events. Neurological complications reported so far in patients affected by new coronavirus infectious disease (COVID-19) probably are not related to a direct neurotropism of the virus and but to its potential ability to induce auto-immunity reactions. Several neurological complications have been described, including cerebrovascular accidents, polyradiculoneuritis (Guillain Barré syndrome), and other inflammatory diseases (Ahmad and Rathore 2020). Among the peripheral nervous system manifestations, the most frequently observed are hyposmia, hypogeusia, and Guillain Barré syndrome (GBS)

(Helms 2020, Zhao 2020, Manganotti 2020). GBS is a heterogeneous condition with several variant forms: the most common presentation is the progressively ascending tetraparesis (acute inflammatory demyelinating polyneuropathy), but other localized clinical variants are also recognized. Miller-Fisher syndrome (MFS), a regional variant characterized by the triad of ophthalmoplegia, ataxia and areflexia, has also been linked to COVID-19 (Manganotti 2020). According to a new classification, autoimmune neuropathies can also include forms with central nervous system involvement (Bickerstaff brainstem encephalitis) (Wakerley et al. 2014). About 60% of the above-mentioned autoimmune syndromes can be infection-related by humoral and cellular cross-reactivity (Lehmann et al. 2010, Pusch et al. 2018), most frequently gastrointestinal (*Campylobacter jejuni*) or respiratory tract infections, including flu syndrome and pneumonia (Sellers et al. 2017, Kim et al 2017). Clinical neurophysiology represents a fundamental tool for the diagnosis of acute inflammatory neuropathies. Neurophysiological investigations, however, require close contact with the patient and may result in an increased risk of infection, therefore only partial data have been collected so far in COVID-19 patients.

### **Cerebrovascular symptoms and post-COVID 19**

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In spite of a lot of unknown facts about clinical and epidemiological implications of COVID-19, there is no doubt that the virus is highly neurotropic. In most of the cases, respiratory or flu-like symptoms are accompanied with loss of olfactory and sometimes gustatory functions. Affection is possibly direct via tractus olfactorius, but as the other mechanisms as increased blood-brain permeability and microglial activation are possible, central nervous system can be affected in a lot of other ways as well. Furthermore, as COVID-19 infection leads to a procoagulative state, micro and macrovascular thrombosis may occur in central nervous system as well, leading to thrombotic angiopathy, vasculitis, encephalopathy and stroke.

Having this in mind, it was actually a surprise that during the first pandemic wave the number of hospitalized patients with stroke decreased. Actually, this was the result of smaller numbers of patients with mild stroke who came to the hospital at all. Longer term statistic showed no significant decrease of stroke, but also not an expected significant increase, for which we do not have explanation yet. In any case, according to the investigation of Berlitz et al, incidence of stroke in COVID-19 patients was only about 1.6 – 5% in Europe, and some authors report even less percentage of stroke patients among hospitalized COVID-19 positive patients, coming even down to 0.9%. However, in all studies hospital stay for stroke patients with COVID-19 infection was longer and mortality higher than in patients who were not COVID-19 positive. COVID-19 positive group of patients had also higher CRP at the admission, and more often diabetes and coronary heart disease as a risk factor than the group of patients without COVID-19 infection.

Considering type of stroke, ischaemic stroke due to small vessel disease occurred more often combined sometimes with diffuse leukoencephalopathy and microhemorrhages.

Some cases of cerebral sinus thrombosis as well as PRESS for no other reason are published in connection with the virus infection as well. Finally, recently more and more patients with non-specific “encephalopathy” and peculiar MRI changes after COVID-19 infection are reported, and causal relationship is discussed as well, with no definite answer for now.

## **Movement Disorders and post-covid-19 neurological syndrome**

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The COVID-19 pandemic has major consequences on our society and way of life and has changed the way we practice neurology, especially movement disorders. We have observed that patients with COVID 19 infections can develop other movement disorders symptoms like myoclonus or confusion and encephalic symptoms. Individuals with Parkinson’s disease (PD- the most often movement disorders) are particularly vulnerable to experiencing the negative squeals, not only because of changed life style, which causes an increased stress and reduction in physical exercise, but also because of compromised respiratory system that put them at higher risk of COVID-19 pneumonia: rigidity of respiratory muscles, common dyspnea and reduced cough reflex. Also, less capability to adopt to new circumstances is a big issue in PD patients. People with PD demonstrated more anxiety and depression as well as decreased levels of quality of life and physical activity as compared to controls during the COVID-19 lockdown. Since PD affects elderly population the risk factors for a more severe COVID-19 presentation in general population. According to the current literature in advanced PD, a rapid worsening of PD could mean onset of COVID-19 infection. Recent studies have shown higher risk for a worse course and outcome. The common risk factors for higher mortality are older age, longer disease duration, use of advanced therapies, dementia, and hypertension. In last year we have developed telemedicine-based communication with our patients.

SARS-CoV2 can cause loss of smell – this is a well-described symptom of COVID-19. Most people who experience loss of smell associated with COVID-19 regain their sense of smell after recovery. And we know that loss of smell can also occur early during PD. However, we do not know whether lack of smell in COVID-19 shares the same mechanism by which loss of smell occurs in PD. It remains unclear therefore, whether the COVID-19 and PD are related or merely share a symptom. Also, there are three case reports in the literature, one of a 45 year old man who developed acute onset parkinsonism in the setting of COVID-19, one of a 35 year old woman who developed parkinsonism after mild COVID-19 infection, and one of a 58 year old man who developed a more complicated parkinsonian syndrome, which subsequently improved, in the setting of COVID-19. Although the Spanish flu was caused by an entirely different virus from SARS-CoV2, it does stand as an example of a primarily respiratory infection associated with delayed parkinsonism as a neurological consequence.

Also, there are studies that recognize the increasing numbers of ex-patients with Post COVID Neurological Syndrome (PCNS). A small number of people who recovered from COVID-19 are reporting neurological concerns such as headache, dizziness, lingering loss of smell or taste, sleep problems, fatigue, muscle weakness, nerve damage,

and trouble thinking or concentrating — sometimes called “COVID fog” or “brain fog”. We need further neurological and cognitive/affective monitoring of all cases of COVID19 (irrespective of the severity from asymptomatic, mild to severe) for PCNS. Global clinical registries with a meticulous systems-based approach to the assessment, management and reporting of post-COVID patients will help us.

In conclusion, for now, the causal association of SARS-CoV-2 infection with the development of Parkinson’s disease is therefore not supported by robust evidence yet. But, the potential neurological sequelae of this novel coronavirus should not be underestimated and must be carefully monitored in the future. A coordinated international effort to investigate viral effects is essential and should be based on well-designed prospective studies. Undoubtedly, we need additional studies to confirm/refute the trigger effect of SARS-CoV-2 on the neuroinflammatory and neurodegenerative processes leading to the development of parkinsonian symptoms.

**Key words:** Movement disorders, Post-covid 19 neurological syndrome, Covid 19 pandemic, Parkinson’s disease