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# Aim and scope

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## Scope of the journal

Founder and the First Editor-in-Chief of the journal has been Professor Jana Zvarova, Prague, Czech Republic who established this journal in the year 2013. The International Journal on Biomedicine and Healthcare (IJBH) is an online journal publishing submissions in English language. The journal aims to inform the readers about the latest developments in the field of biomedicine and healthcare, focusing on multidisciplinary approaches, new methods, results and innovations. It will publish original articles, short original articles, review articles, case reports, and short format articles reporting about advances of biomedicine and healthcare, abstracts of conference submissions, case-studies and articles that explore how science, education and policy are shaping the world and vice versa, editorial commentary, opinions from experts, information on projects, new equipment and innovations.

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# Why Registering Your Research Study Involving Human Subjects Before Its Onset?

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**Background:** The World Medical Association's Declaration of Helsinki explicitly requires registration of a study involving human subjects before its onset. The registration creates an opportunity for improvement of design and avoidance of bias. **Objective:** The aim of this article was to elaborate a need for creating regional registry of clinical studies for Balkan countries. **Methods:** Available international, national and regional registries were searched for in PUBMED database and by general purpose search engines like Google or Yahoo. The following types of publications were included in the survey: original studies, case studies, case reports, narrative reviews, commentaries and expert opinions. **Results.** The most important international registries of research involving human subjects are „ClinicalTrials.gov“ dabase of US National Institute of Health, the World Health Organization's „International Clinical Trials Registry Platform“, PROSPERO and Cochrane Database of Systematic reviews and meta-analyses, and the Research Registry, focusing on observational studies. National registries were established in Japan, South Korea, Sri Lanka, China, and others countries, while European Union has the most elaborate of regional registries. National and regional registries performe better than large international ones: the registrations are more complete, and researchers are more aware of their obigation to pre-register a clinical study. **Conclusions.** There is great need for one regional registry of clinical studies for Balkan countries, which would suit well the whole region, considering great socio-economic, cultural and lingual similarities of the Balkan countries.

**Key Words:** Clinical study; Registry; Risk of bias; Transparency

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## 1. INTRODUCTION

Registering a study involving human subjects before its onset is a requirement imposed by the World Medical Association's Declaration of Helsinki – Ethical Principles for Medocal Research involving Human Subjects, version 2013 (1). In the article 35 of this declaration is explicitly demanded: „Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.“ At first, only clinical trials, i.e. experimental studies involving human subjects were registered in a „ClinicalTrials.gov“ dabase of US National Institute of Health (2); the database was launched in year 2000, and later on started with registration of observational clinical studies, too.

World Health Organization established its register of clinical trials entitled „International Clinical Trials Registry Platform“ (ICTRP) in 2005 (3). Systematic reviews and meta-analyses are pre-registered in PROSPERO database, founded and kept active by University of York Centre for Reviews and Dissemination, United Kingdom (4), or in Cochrane Database of Systematic reviews, if part of the Cochrane collaboration (5). The most recent global

initiative is Research Registry, launched in 2015 and registering all types of both experimental and observational clinical studies (6).

Main reason for registering a clinical study protocol before initiation of the study is transparency: anyone interested should have access to the protocol and check methodology issues. It is methodology of a study that reflects its quality; only if basic research principles are fully implemented in the study design, a reader may trust to the results obtained.

Therefore, the first benefit of registering and making study protocols visible to everybody is ensurance of sufficient methodological quality, which is achieved by review and revisions of the protocols prior to their registration and publication (7). Second, other investigators within the same field may become aware of ongoing studies and avoid duplicating the same design. Third, the results that will be published in future could be matched to original study design, and any discrepancies or posthoc manipulations revealed. Finally, if results of the registered studies are added to the records after their completion, even if they are not published in a journal, they will be

accessible to research community; it is especially important for studies with negative results, i.e. where difference among the study groups was not significant, since majority of medical journals avoid publication of such results.

## 2. IMPORTANCE OF HAVING REGIONAL REGISTRIES

Although several registries for pre-registration of studies involving human subjects already exist on global level, there are certain weaknesses derived from their global character. If a registry accepts studies from all over the world, inevitably number of registrations will be large and will grow exponentially (e.g. Research Registry after only five years of functioning has more than 5000 registrations) (8); if founders of the registry are not having sufficient funds to heavily invest in peer review of the submitted study protocols, the registration may become purely formal and lose its intended benefits. Another weakness is limited amount of information about the registrants which depend on her/his frankness and honesty; without knowledge about the research context and state-of-art in healthcare and research milieu where the study proposal comes from, it is difficult to recognize methodological errors, research misconduct or possible ethical issues.

Regional or national research registries were established in a number of cases, and their functioning was associated with improvement in both quantity and quality of clinical research within the areas covered. Researchers rapidly became aware of regional registries, and majority complied well with requirements and standards of registering clinical studies, although periodic audits are still necessary for full adherence (9). National registries of clinical studies were established in Japan back in 2005 (10), in Sri Lanka in 2010 (11), South Korea (Clinical Research Information Service), and many other countries, while regional registry of clinical trials was founded in European Union (European Clinical Trials Registry (EuCTR)) (12). It is interesting that small national registries performed better than large international ones: the registrations were more frequently complete in small registries, and researchers were more aware of national or regional registries than of international ones (11).

Researchers in Balkan countries are even less aware of international registries involving clinical studies, and of Helsinki declaration's recommendation that all studies on human subjects should be registered prior to enrollment of the first patient. Recent survey of transparency and visibility of clinical trials in Croatia (13) was concentrated on potential users of reports registered at previously mentioned international registers of clinical investigations. It showed that, although registered in international registries, they are not visible to patients and probably to researchers that work on other types of clinical studies, apart from randomized clinical trials. The importance of visibility of ongoing clinical trials or studies

in general for patients who are potential study subjects could not be overestimated. Recruiting sufficient number of study participants is not an easy task even when disorders that are studied occur with high frequency in general population (e.g. asthma or diabetes mellitus), and it becomes very difficult when a disease studied is rare or associated with impairment of consciousness or cognition. Clinical trials are mostly done in tertiary care health facilities with limited number of beds and staff that is already engaged in other activities. In the same time there are dozens of ongoing trials, so it is of vital importance that potential participants know what studies are active and where they could be enrolled to receive an investigational, but potentially curable treatment.

There are several reasons why researchers should be well acquainted with ongoing and completed clinical investigations. The first is to avoid unnecessary duplication of research efforts, and to modify own study pro-

Title of the research project	
The study acronym	
Principal investigator and his (her) affiliation	
List of other investigators with e-mails and affiliations	
Sponsor of the study, if any:	
Study design (underline the applicable)	Interventional study
	Cohort study
	Cross/sectional study
	Case/control study
	Meta-analysis or systematic review
Qualitative study	
Study design – further specification, if applicable (e.g. double-blind, randomized, controlled clinical trial, nested case/control study, etc.)	
Time and place of the study conduct	
Study population (inclusion, non-inclusion and exclusion criteria)	
Size of the study sample (calculation method, inputs and result)	
Sampling method (random, convenience, etc.)	
Methods of literature search (for meta-analyses and systematic reviews only)	Who will perform the search
	When
	Source databases
Search strategy	
Primary outcome of the study	
Secondary outcomes of the study	
Presumed independent variables	
Confounders	
Planned statistical processing	
Ethics committee or Investigation research Board that will evaluate the study	
Funding source, if any	
Measures for controlling bias	
What novelty will the study bring?	
Could results be applied (generalized) to other populations or patient groups?	
How the results will affect healthcare?	

Table 1. Proposal of the clinical study registration form.



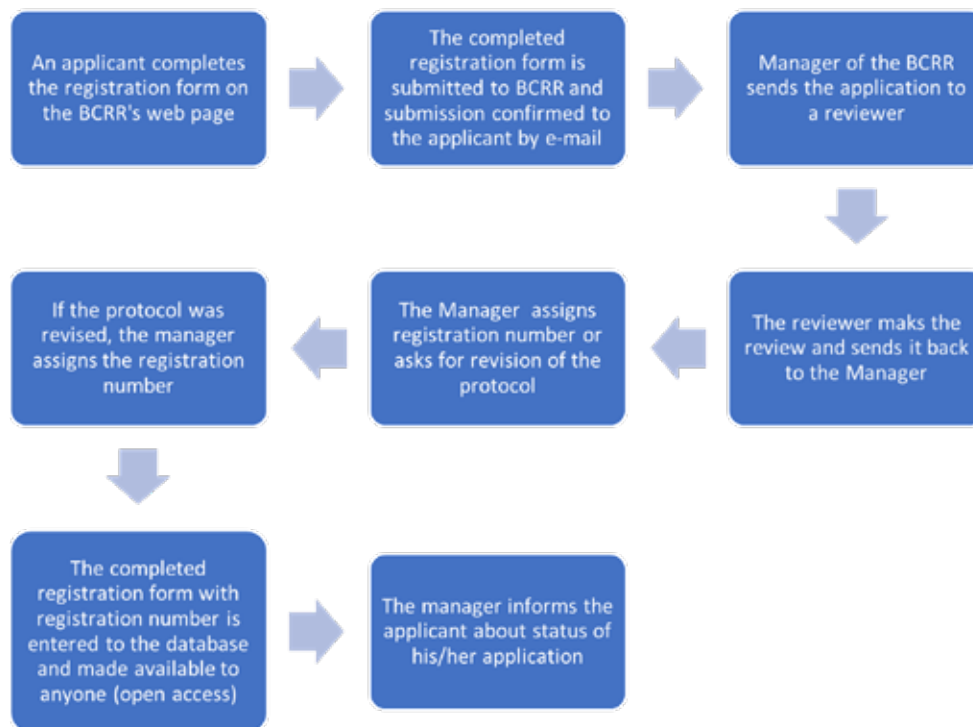


Figure 1. Algorithm describing functioning of the BCRR.

tolcol maintaining novelty of potential findings. The second reason is potential of collaboration with investigators of already ongoing studies: clinicians may want to include their regular healthcare patients in such studies, in order to receive promising investi-gational drugs, especially if all standard therapeutic options are exhausted. Third issue is help when designing new study within the same therapeutic area as already registered trial. It is extremely useful to read through data of registered studies and get an insight in outcomes worthy of following and variables of significance that should be taken into account. Choice of study groups and statistical tests is also crucial, and registered studies may offer important suggestions.

In general, Foundation and successful operation of a registry of clinical studies only for Balkan region would be of great help to regional researchers, giving them chance not only to register their research, but also to improve it through preregistration peer review and useful advices how to avoid bias and methodological errors.

### 3. AN INITIATIVE TO ESTABLISH BALKAN CLINICAL RESEARCH REGISTRY (BCRR)

If we agree that regional clinical research registry is necessary to all Balkan countries, it seems the most plausible to establish it under some respectful regional scientific organization that is both open to everyone in the region and independent from financial and political power

centers. The Academy of Medical Sciences of Bosnia and Herzegovina (AMSBH) could be an ideal choice, due to its high scientific standards, multicultural and multinational character of society in Bosnia and Herzegovina and its openness to all countries within the Balkan region. The AMSBH may establish the registry by decision of its assembly, and create its electronic form on a reliable server with suitable web-page that will include registration forms, necessary instructions and other information important for functioning of the registry. Modus operandi of the BCRR could be like the proposal described at Figure 1, and one possible version of the registration form is shown in the Table 1.

### 4. CONCLUSIONS

Registration of clinical studies before their commencement increase transparency of methodological issues and creates an opportunity to improve design and decrease risk of bias. Although there are numerous international registries, there is great need to have national and regional options too, which make researchers more aware and compliant to obligation of pre-registrering clinical studies. One regional registry of clinical studies for Balkan countries would suit well the whole region, considering great socio-economic, cultural and lingual similarities of the Balkan countries.

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# Will COVID-19 Pandemic Produce Stronger Consequences than Spanish Flu Pandemic?

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**Background:** The Spanish flu of 1918 and 100 years later, the COVID-19 pandemic, paralyzed the entire world, causing numerous casualties and halting life flows. Although there is a hundred-year gap between them, the facts indicate that both pandemics are of viral origin, which primarily attack the respiratory system, but affect different age groups, have a similar course, different mortality. 20-50 million people died from the Spanish flu and 1.6 million from COVID-19. Prevention has remained almost the same after 100 years. **Objectives:** The aim of this article is to evaluate new findings on COVID-19 based on the Spanish flu paradigm, comparing these two pandemics. including scientific research in the field of virology and epidemiology related to this issue. **Methods:** The available literature was searched and facts analyzed using the keywords: Spanish flu, COVID-19, commenting on the results of scientific studies according to the EBM, regarding the prevention and treatment of the COVID-19 pandemic. **Results and discussion:** Numerous pieces of evidence unequivocally prove that these are viral pandemics caused by different viruses, Spanish flu with H1N1 virus and COVID-19 with SARS-CoV-2 virus. Two waves of the epidemic COVID-19, the second, despite measures taken, surprises with intensity and speed of spread. With numerous human casualties and huge economic suspensions, there are still many unanswered questions regarding the clinical picture, the unpredictability of development of the disease, the rate of virus mutation, access to treatment and vaccination. **Conclusion:** Comparing the two pandemics, the one from 1918 (Spanish flu) and today's, COVID-19, a hundred years later it is clear that the former had a significantly higher number of victims, compared to today (20-50 million : 1.6 million). Economic losses are immeasurably greater during the COVID-19 pandemic, and the scale of the economic catastrophe will add up years later. The consequences of lockdown, the loss of loved ones, the consequences of illness, economic uncertainty, job loss, fear of an impending epidemic are numerous mental illnesses, depression, in short - life before and after COVID-19 will never be the same again.

**Keywords:** Spanish flu, COVID-19 pandemic.

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## 1. BACKGROUND

And as COVID-19 dances his „Danse Macabre“, we notice with fear the scale of the catastrophe that has befallen the world. COVID-19 doesn't make choices, it spreads linearly, so whoever gets hooked, and it seems there are no rules. Personally, at the beginning of the pandemic, like a lot of colleagues I have contacted, we thought it was a seasonal infection that would go away on its own. However, shocking images from Italy, Spain, then from the U.S. and around the world revealed the scale of the pandemic and its deadly potential. And when COVID-19 rips family members out of our lives (even in my own family!) And people who were healthy and followed recommendations, then you realize that COVID-19 is a dangerous monster that devours human lives and is by no means a „funny virus“ as it was named by one colleague. In COVID-19, there are cer-

tain legality: it does not attack children and younger age groups, although they are not completely spared. What is obvious is that most of the victims are those who have passed two thirds of their lives, especially those at the end of their lives, patients without immunity, patients with malignant diseases. To understand the current situation with COVID-19, we will recall the world's largest (viral) epidemic in 1919, popularly called Spanish flu.

## 2. SPANISH FLU PANDEMIC

The Spanish flu, also known as the 1918 flu pandemic, was an unusually deadly influenza pandemic caused by the H1N1 influenza A virus. Lasting from February 1918 to April 1920, it infected 500 million people – about a third of the world's population at the time – in four successive waves (1). It is useful to compare COVID-19 with the



epidemic of 1918-19, when the „Spanish flu“ was rampant. Comparing both diseases of the same (viral) origin, but different types of viruses (H1N1: SARS-CoV-2), with a similar clinical presentation, similar in appearance, during infection, we notice that modern medicine in terms of prevention (mask, distance, disinfection, isolation, quarantine) and treatment has not advanced much since that time, although the achievements of modern medicine are immeasurable. The fact that, according to various authors, 20-50 million people died from Spanish flu (the exact data will never be known) shows the scale of the catastrophe that affected the world at that time. The scope of the medicine of that time should be taken into account, when viruses were not even known and there were no antibiotics, it all came down to treatment of symptoms (fever, analgesics, supportive measures). It is assumed that a bacterial infection was grafted onto the viral, which explains the extremely high mortality from this disease.

The very name „Spanish flu“ is dubious because its source was not in Spain but in the United States, more precisely in Boston. As in I World War, Spain was neutral, had a liberal press and wrote the most about the flu that took lives. On the other hand, other war-torn countries banned writing about the disease believing it was lowering the morale of soldiers, so the media buzz about the flu in Spain spread to the world leading to the flu being popularly called the Spanish flu (2).

Even then, euphemistically, it was considered that it is a „stronger flu“, as what happened is same as today: the rapid spread of the epidemic and the collapse of the health system. The measures of (self) protection at that time were a copy of today's (masks, disinfection, distance). Isolation measures were also similar to today's: restricting gatherings, closing borders, institutions, theaters, schools. Finally, the foundation of isolation in case of infectious diseases was a measure from the Middle Ages, quarantine, which was a barrier to the spread of infectious diseases. For example, passengers had to be quarantined for 40 days to avoid spreading the infection. It is worth mentioning that in 1377, Dubrovnik was the first city in the world to introduce quarantine.

Also, then, during the Spanish flu, all public places were disinfected, and in the United States, draconian fines were paid, the then \$100 fine for not wearing a mask. In 1918, it was quickly realized that mass gatherings, crowds, socializing, and meetings could cause a rapid transmission of the infection.

For example, in the city of Zamora in Spain, the bishop called for a mass that contributed to the pandemic, and the San Isidro Festival was held in Madrid, in the USA in Philadelphia in 1918, the Loan Parade, which resulted in thousands of infected with Spanish flu.

Officially, the onset of the flu dates back to March 11, 1918, when a military cook at a U.S. base in Kansas reported to a doctor at a Fort Riley hospital complaining of cough, headache, and fever. According to these general symptoms, the doctor concluded that it was the flu. However, by lunch the hospital already had about a hundred soldiers

with the same symptoms and by the end of the week that number had risen to 500. At the end of the month, so many soldiers reported that the hospital was too small to accommodate them, which is why the military command repurpose aircraft hangar in the hospital.

The flu occurred in three waves, the deadliest of which was the second wave, when mortality was highest. In the flood of articles about the Spanish flu, the book by British investigative journalist Laura Spinney stands out in her book „The Pale Rider: The Spanish Flu in 1918 and How It Changed the World“. The book methodically analyzes all the details related to the origin of the flu and its course, and its end after one year. The book, published in 2018, is the most comprehensive document on the most terrible epidemic that has befallen the mankind (3).

None of the pandemics of the past can be compared to the Spanish flu that reached every corner of our planet (except Antarctica) and affected 500 million people, which was a third of the Earth's population at the time. The hardest hit country was India, where the flu killed 17 million people and was the trigger for strengthening the movement against British colonial rule.

Unlike the seasonal flu that we encounter every year, which is most dangerous for children, the elderly and people with impaired immunity, the Spanish flu mostly attacked young and healthy people between the age of 20 and 40. Infected people would die very quickly, sometimes just hours after realizing they were sick. The first symptoms were fatigue, high fever and headache, followed by muscle and joint pain. However, the symptoms would worsen drastically in a few hours. The sick died in the most severe torments: their skin would turn purple, later on autopsy, their lungs would be filled with a reddish gelatinous mass that would slowly suffocate them. Due to the cough intensity, some patients had torn abdominal muscles. The cause of death was usually bleeding from the mucous membranes, especially from the nose, intestines and stomach.

The sinister Spanish flu attacked humanity in three waves. The first was recorded in March 1918 when a virus struck U.S. troops in Kansas. Mortality in that wave was not so high, soldiers described it as a „three-day fever“, and by the end of the spring it had taken 56 lives. But the problem was that American soldiers were going to Europe, so the flu spread across the Old Continent. The second wave of the Spanish flu was the deadliest, occurring in August 1918. The first to be hit were the cities of Boston and Philadelphia in the United States, Brest in France, and Freetown in Sierra Leone. The third wave of the Spanish flu started in early 1919 and lasted until March 1920. Fortunately, it was not as deadly as the second wave, which, according to some estimates, took 25 million lives in 25 weeks. Many famous people in the world were killed by the Spanish flu: the French poet Guillaume Apollinaire, the Austrian painter Egon Schiele and his family, who left behind a shocking image of his ailing family, then the Donald Trump grandfather (4).

As for the nature of the vicious virus, we learned more

about a decade ago when Canadian scientists pulled the body of one of the victims of the Spanish flu from a mass grave in Alaska. They then extracted and preserved the genetic material of the virus. Subsequently, in the complete safety of the Canadian Microbiological Laboratory, they reconstructed the effective H1N1 virus. They infected macaque monkeys with it to investigate the development of the disease. The result was a terrible reaction of the organism, the first symptoms of the disease appeared after 24 hours. The destruction of the lungs that followed was so dramatic that the monkeys would have suffocated in their own blood had they not been euthanized. These results are very similar to the descriptions of the disease from the time of the pandemic. Studies have shown that such severe lung damage was not directly caused by the virus itself, but by a defensive reaction of the organism to the infection. Namely, significantly higher levels of protein are detected in the lungs of monkeys, which causes the destruction of infected tissue than is usual in other viral diseases. Of course, Canadian researchers, because of this daring experiment that could be potentially fatal if the virus „escaped“ from the laboratory, were under fierce criticism (5).

Experts from the World Health Organization (WHO) and the U.S. Center for Disease Control and Prevention (CDC) in Atlanta believe a new flu pandemic is if not inevitable, then certainly probable. If humanity were hit by a virus that would be similar in its lethal potential to that of 1918, between 20 and 100 million people would die. It sounds scary, but compared to 1918, there are still drugs today, and a vaccine has just been approved, which can significantly alleviate the scale of the pandemic, in the most optimistic forecasts, and eradicate the pandemic.

### 3. PANDEMIC CAUSED BY CORONA VIRUS SARS-2

The corona virus, officially named SARS-CoV-2, as the cause of the infectious disease COVID-19 in a short time from December 2019 until today has caused a pandemic that has affected the entire world with extremely high mortality. Here is the data from December 11, 2020:

- Laboratory confirmed cases of COVID-19 disease worldwide (source ECDC): 69,282,662.
- Worldwide deaths (ECDC source): 1,582,381.
- Number of cases in Europe (EU/EEA and UK - ECDC source): 14,651,551.
- Deaths in Europe (EU/EEA and UK): 365,293.
- Number of patients in Croatia: 168,388.
- Number of deaths in Croatia: 2,484.

After China, the pandemic hit Europe hard, followed by the United States, which has had a continuous increase in the number of cases since the beginning of April, with the largest weekly increase in the number of new cases. This makes the U.S. the most affected country, accounting for more than 30% of all confirmed COVID cases to date. Unemployment in the world is rising, and the International Monetary Fund has declared this crisis the biggest since the Depression in the 1930s. This situation has forced

many countries to close their borders for the first wave of the pandemic and apply variously strict epidemiological preventive measures. Most countries have implemented a complete lockdown within a few weeks, with a ban on movement, gatherings, working from home, closing kindergartens, schools, colleges, public spaces, parks, service activities, urban and interurban traffic. International air traffic has been minimized, millions of people have lost their jobs, the world economy has slowed sharply with a vague prospect of recovery. In the second wave, similar to the Spanish flu, high numbers of patients are repeated, so even more rigorous isolation measures are being prepared, all the way to the lock down. Finally, much more is unknown about the virus for which the vaccine has just been registered from several different companies from different countries, and vaccination has just started in the UK (6).

### 4. CLINICAL PICTURE AND DISEASES FLOW

(According facts and recommendations of WHO experts).

As for the clinical presentation, COVID-19 is an epidemic viral disease in which the most common symptoms are: fever, dry cough and fatigue. Other symptoms that are less common but typical of COVID include: primarily loss of taste or smell, then nasal congestion, conjunctivitis (also known as red eyes), sore throat, headache, muscle or joint pains, various types of rash on skin, nausea or vomiting, diarrhea, shivering and dizziness. Symptoms of severe COVID-19 disease include: shortness of breath, loss of appetite, confusion, persistent chest pain or pressure, and high fever (above 38° C). Other less common symptoms are: irritability, confusion, decreased consciousness (sometimes associated with seizures), anxiety, depression, sleep disorders, severe and rare neurological complications such as stroke, encephalitis, delirium and nerve damage. People of all ages who have a fever and/or cough associated with shortness of breath or difficulty breathing, chest pain or pressure, or loss of speech or movement should seek medical attention immediately. If possible, call your doctor, emergency room, or health care provider for treatment.

As for the course of the disease, among those who develop symptoms, the majority (about 80%) recover from the disease without the need for hospital treatment. About 15% are seriously ill and need oxygen, and 5% are critical and need intensive care and a mechanical ventilation. Complications leading to death may include respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including heart, liver or kidney injury syndrome few weeks after infection. Unfortunately, in the most severe cases requiring mechanical ventilation, mortality is extremely high, with recent data showing that about 70% of cases have lethal outcome (7, 8).

People aged 60 and over, and people with comorbidities such as high blood pressure, heart and lung problems, diabetes, obesity or cancer, are at higher risk of developing

a serious illness. However, anyone can get COVID-19 and even the most severe form of the disease or die at any age (9).

## 5. DIAGNOSTICS OF COVID-19

a) In most cases, a molecular test is used to detect SARS-CoV-2 and confirm infection. Polymerase chain reaction (PCR) is the most commonly used molecular test. Samples are taken from the nose and/or throat with a swab. Molecular tests detect the virus in the sample by amplifying the viral genetic material to detectable levels. For this reason, a molecular test is used to confirm an active infection, usually within a few days after exposure and approximately the time when symptoms may begin.

b) Rapid antigen tests (sometimes known as rapid diagnostic tests - RDTs) detect viral proteins (known as antigens). Samples are taken from the nose and/or throat with a swab. These tests are cheaper than PCR and will offer results faster, although they are generally less accurate. These tests are best performed when multiple viruses are circulating in the community and when samples are taken from an individual at a time when they are most contagious.

c) Antibody tests can tell us if someone has had an infection in the past, even if they have had no symptoms. Also known as serological tests, and usually done on a blood sample, these tests detect antibodies that are produced in response to an infection. In most people, antibodies begin to develop after a few days or weeks and can indicate whether a person has had a past infection. Antibody tests cannot be used to diagnose COVID-19 in the early stages of infection or disease, but they can indicate whether someone has had the disease in the past. (10)

## 6. PREVENTION MEASURES AGAINST COVID-19

At the level of countries, in the first outbreak of COVID-19, when it was seen how dangerous the virus is and when the pandemic was rampant, all countries of the world introduced certain degrees of lockdown, trying to suppress the intensity of the infection (11).

Isolation and quarantine are methods of preventing the spread of COVID-19. Quarantine is used for anyone who comes in contact with a person infected with SARS-CoV-2 virus, which causes COVID-19, regardless of whether the infected person has symptoms or not. Quarantine means that you remain separate from others because you have been exposed to the virus and may be infected and can take place in a designated facility or at home. For COVID-19 this means staying in the facility or at home for 14 days. Isolation is used for people with symptoms of COVID-19 or who have tested positive for the virus. Being isolated means being separated from other people, ideally in a medical facility where you can get clinical care. If isolation in a medical facility is not possible and if you are not at risk for developing a serious illness, isolation can occur at home. If you have symptoms, you should remain isolated for at least 10 days plus an additional 3 days

without symptoms. If you are infected and do not develop symptoms, you should remain isolated for 10 days from the time you receive a positive test (12, 13).

## 7. TREATMENT OF COVID-19 INFECTION

As stated in the Spanish flu reviews, unfortunately, there is no causal therapy for COVID-19 as it is for most viral diseases after all. Therapy is primarily symptomatic, in mild cases (antipyretics, analgesics, symptomatic and supportive therapy) and in the presence of signs of associated bacterial infection antibiotics. In the most severe cases, hospital treatment in intensive care units, corticosteroids, broad-spectrum antibiotics, oxygen therapy, and finally, mechanical ventilation are indicated. In the first wave of infection, Remdesivir was labeled as a promising drug, and later was rejected as standard therapy for the treatment of COVID-19. Unfortunately, as noted, in patients with respiratory disease mortality is extremely high and rises up to 70% (14-16).

## 8. DILEMMAS REGARDING COVID-19 PANDEMIC

Finally, issues related to coronavirus infection remain unresolved:

a) Why do only some people develop severe forms of the disease?

b) Why do one or two members of the bloodline family members die in the same family (e.g., father and son, mother and daughter) and the spouse is spared?

c) How to interpret that, unlike the Spanish flu when the group of those in full strength at age of 20-30 years was most affected, but also children, then old, while in COVID-19, the distribution of patients is most often in those over 60 and children are spared?

d) Why, despite all the measures taken, has the pandemic not been eradicated?

e) Is the vaccine a way out of the vicious circle?

f) What will be the economic indicators of the COVID-19 pandemic?

g) How will the pandemic affect the mental health of nations?

There is no clear answer to the first three questions, but the available literature assumes that the cause is a congenital, inherited defect in the immune response in some individuals, and the aforementioned cytokine storm, (i.e., a hyperinflammatory response to infection). The answer to the third question is unknown, but the cause is a probable mutation of the virus that affects the target groups. The reason why, despite all pandemic measures, has not been stopped is the fact that today the connection of countries is such that the infection from one country can be transmitted to another continent on the same day. In addition, non-compliance and strong resistance of individuals to the recommended measures of (self) protection should be stated. Apparently, the vaccine seems to be the promised light at the end of the tunnel. As far as the economies of the countries are concerned, it is certain that everyone will have a marked decline in GDP with a significant de-



cline in production, which will be felt for years, the loss of jobs. This in turn leads to poverty, declining quality of life, mental illness and depression.

## 9. CONCLUSION

It is really difficult today to arbitrate on everything that has been done to combat the pandemic. Because, despite the WHO recommendations, some countries have their own national strategy and models of approach to the pandemic (e.g., Sweden, the Netherlands, the USA...) so the approach to solution is not uniform. The only right path is the opinions and recommendations of the WHO and the application of evidence-based medicine. The importance of the protective triad has been accepted by the plebiscite since the time of the Spanish flu (masks, distance, isolation...). Nevertheless, strong resistance and protests have been expressed in many countries over the measures taken, all under the auspices of restrictions on human freedoms. So, the numerous movements arose: maskers and antimaskers, vaxxers and anti-vaxxers, civil disobedience, all largely due to fake news, and fantastic conspiracy theories. At the same time, with incomprehensible resistance to the efforts of the scientific community to get out of the vicious circle that leads to the collapse of the economy of all countries. The use of the vaccine (partly challenged by the so-called anti-vaxxers movement) has been plebiscitarily accepted by the WHO as the only real way out of the hell of a pandemic. Alternatively, to fight only the current measures that have not (for known reasons) managed to curb the infection or the promising vaccination that would radically interrupt the course of the epidemic is the only right choice and for salvation for the world. Comparing the two pandemics, the one from 1918 (Spanish flu) and today's, COVID-19, a hundred years later it is clear that the former had a significantly higher number of victims, compared to today (20-50 million : 1.6 million). On the other hand, economic losses are immeasurably greater during the COVID-19 pandemic, and the scale of the economic catastrophe will add up years later. The consequences of lockdown, the loss of loved ones, the consequences of illness, economic uncertainty, job loss, fear of an impending epidemic are numerous mental illnesses, depression, in short - life before and after COVID-19 will never be the same again.

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# The Importance of Nutrition in Boosting Immunity for Prevention and Treatment COVID-19

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**Background:** Multiple Life and health directly depend on food and normal digestive system functions, as well as eating habits. Absorbed essential and beneficial nutrients from food are used by all human organic systems to maintain their functions for the purpose of maintaining health. The immune system resists harmful agents from the environment and increases level of its activity during infection. Such activity requires more energy sources and specific substrates from food to activate cellular and biochemical elements of immune defense. Adequate food choices and a wide range of nutrients are necessary to maintain optimal immune system function. In the fight against the COVID-19 pandemic, little attention is paid to strengthening the natural abilities of the human body and its immune system to prevent COVID-19. **Objectives:** The goal of this article is to evaluate new findings on the impact of food, specific nutrients and eating habits on immune system function during the COVID-19 pandemic. **Methods:** The available literature was analyzed using the key words: food, immune system, COVID-19, and the results of studies that have scientific evidence (EBM) for the positive impact of food on the activity of the immune system during this disease were summarized. **Results and discussion:** Food, diet and digestive function play the most important role in the overall immune response to viral infections. It has been proven that the active ingredients of food can strengthen or weaken the immune system (immunomodulation or immunosuppression). Organic balanced food adapted to each person (personal diet) is the first condition for creating an adequate natural defense system. **Conclusion:** There is evidence that many nutrients have key roles in boosting immune system. Strong immune system with adequate response can stop virus entering deeply in human body („to stop virus on the gate“).

**Keywords:** COVID-19, nutrition, immunity, vitamin D.

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## 1. BACKGROUND

The new SARS-CoV-2 virus has spread across the planet to all parts of the world at a rate that has not been recorded in the history of epidemic diseases. The virus caused the disease COVID-19 which led to unprecedented changes in the lives of all people of the world (Figure 1).

Corona viruses represent a generic name for a broad family of RNA viruses that often cause diseases in animals. The first disease in humans was described only at the beginning of this century as a severe form of acute respiratory syndrome (SARS), and the isolated virus was called SARS-CoV. The virus belongs to the RNA group of viruses that have a single-chain genome form. These types of viruses mutate easily, making it difficult to the person's specific immune system to produce adequate re-

sponse to infection or vaccination. The steady increase in the incidence of disease and deaths, worldwide, without significant prevention and treatment options has led to dramatic changes in the economic, political, cultural, sports and other social spheres of every society. This additionally affected the health status, not only of the individual person, but also of all communities, and the entire world population. The COVID-19 pandemic, with its scale and immediate consequences, has caused both pandemic fear and concern among all people of the world (Figure 2).

The World Health Organization (WHO) and public health institutions, using experiences from previous pandemics, are developing different strategies: early interventions with hygiene recommendations, wearing masks, physical distancing, blocking traffic, restrictions



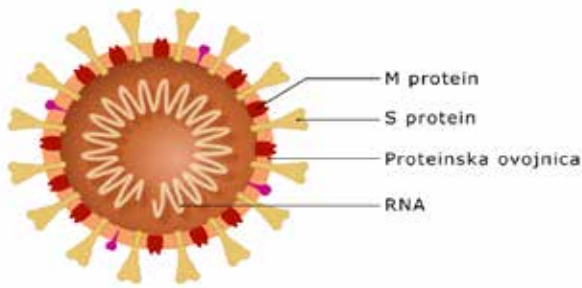


Figure 1. Morphological structure of SARS-CoV-2 virus.



Figure 2. Fear and concern of all people of the world

on movement, quarantine, bans on mass gatherings, closures of schools, universities, bans on cultural and sports events, museums, libraries, factories and other institutions to control the spread of COVID-19 infection. Despite

ening the natural ability of the human body to resist the entry of the virus into human organs and early activation of the immune response with elimination of the virus before the virus enters the cells of vital organs and uses genetic material for its replication. Before the medicine as a science and health systems in the service of population health care, managed to produce and apply many drugs for the treatment of infectious diseases, natural defense managed to overcome many earlier epidemics by strengthening immunity. It is common knowledge that in order to defend against viral infections, humans during the development and maintenance of the species has managed to establish a natural defense against enemies such as bacteria and the viruses. The immune system of new generations recognizes pathogens at earlier stage and enabled efficient specific defense with memory recognition of the antigenic structure of the attacker. The current modern lifestyle with unhealthy diets, along with physical inactivity and stressful working conditions, has led to pandemics of obesity and chronic non-communicable diseases that have significantly affected the functional capacity of the immune system and in some manner facilitated such rapid spread of coronavirus. Modern medicine successfully treats most malignant diseases, including hematological and autoimmune diseases, but such patients are not immunocompetent to defend against the virus and have a predisposition for infection and the development of diseases with complications. There is another type of disease that anatomically affects the entry points for the corona virus, and these are the initial parts of the respiratory and digestive systems. In such diseases, the mucous membranes of the nose, mouth, throat,

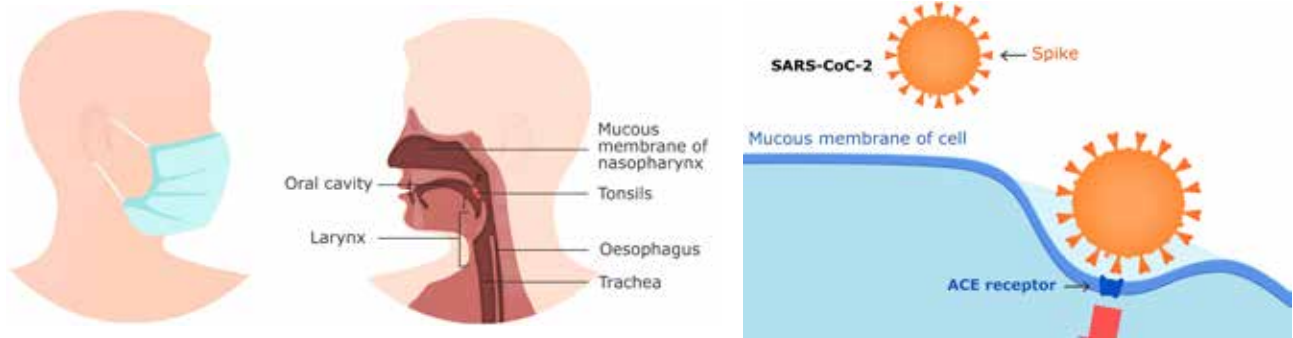


Figure 3. Mechanical barrier and strong mucosal immunity can stop the virus at the gates.

all the efforts, the engagement of experts from all scientific and health institutions, has not polluted, so far, an effective cure for COVID-19. Stopping the pandemic was not done at an early stage so, even a year after the registration of the first case of infection in Wuhan, China, the prevention of the virus spreading has failed. Most of the health systems of the countries of the world had the possibilities of early diagnosis, but they did not have adequate equipment, adequate hospital facilities and educated staff, so even now the pandemic is still in full swing. New drugs and vaccines have an uncertain future. In the fight against this pandemic, little attention is paid to strength-

larynx, and small intestine are damaged, which the virus uses to enter the body more easily. Strengthening the non-specific natural mucosal immunity of the respiratory and digestive systems through healthy lifestyles and nutritional interventions can prevent the virus from penetrating epithelial cells and replicating.

The meet of the virus and the host-human is a dramatic process with an uncertain outcome, and it depends on the degree of virulence and aggressiveness of the virus itself and the strength of human natural defense. For now, humans cannot directly influence the properties and structure of the virus itself, because it is unknown, and we do

not have a specific adaptive immune response. The SARS-CoV-2 virus has an advantage in this first encounter because it has the genetic keys to enter human cells, and the ability to block a specific immune response.

Humans in such cases of contact with new unknown viruses are left to strengthen the natural defense at the gates, where the virus attacks until specific drugs and vaccines are discovered.

If natural immunity fails, a specific, adaptive immunity is activated, which must involve the entire human immune system. Natural inborn immunity can fail more often in the elderly, people with increased body weight, diabetes, insulin resistance, heart and lung diseases. These individuals typically have lower interferon production, fewer virus killer cells, and cells that transmit information (dendritic cells) about virus specifics, and these are very important data needed to produce specific antibodies to eliminate SARS CoV 2. Interaction between first natural immune response and acquired adaptive with specific antibodies and anti-inflammatory cytokines is a key moment for the further clinical course of the disease. The time from the sending of the information about the virus, to the final specific immune response, takes several days. This period is a critical point, because if it lasts longer, the virus crosses the first line of defense and threatens all vital organs, which can lead to multiorgan failure and death. In children, this period is shorter, and the disease occurs in a milder form or even without symptoms. Compromising the adaptive immune response with B and T lymph cells leads to disease complications, cytokine storm, anatomical and functional changes on the alveocapillary membrane that block the exchange of gases between the alveoli and blood vessels. Such a condition with a hyperactive immune response is called ARDS (acute respiratory distress syndrome), which further causes multiorgan failure and often fatal outcome. T and B cells of the lymphatic system in children are also formed in the thymus, so their specific and adaptive response is very rapid. B lymphocytes recognize antigen and produce specific antibodies (immunoglobulins). T lymphocytes have two types of T cells that coordinate the entire immune response: (Helper T cells) and killer T cells that directly destroy the virus (Figure 4).

Immunity is significantly dependent on diet and may

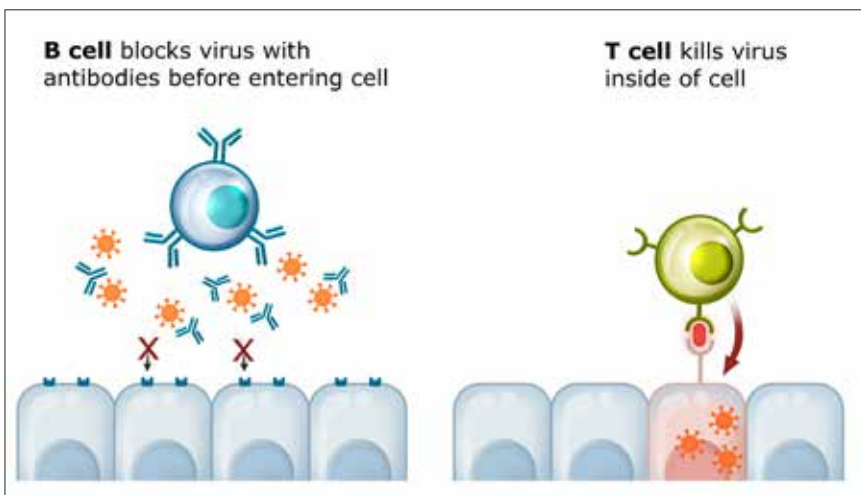


Figure 4 Specific (adaptive) immune response of a cell to the corona virus

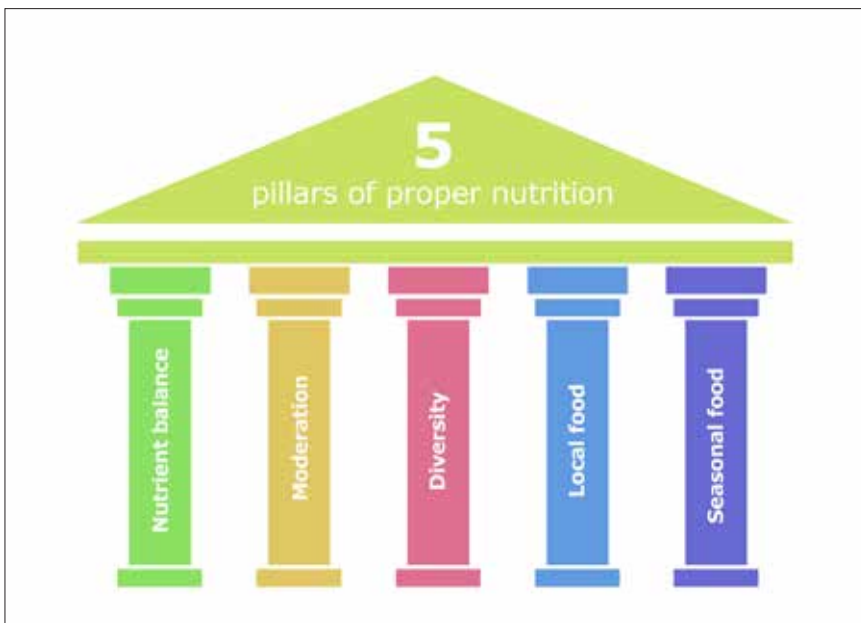


Figure 5. Basic principles of healthy diet in a patient with COVID-19 infection

have an impact on cellular immunity, phagocyte function, cytokine production, secretory response, and antibody activity. In order for food to have an appropriate impact on strengthening immunity, the basic principles of a healthy diet must be met, namely: a variety of seasonal and local foods with balanced essential nutrients in moderation and at regular times.

Life and health directly depend on food and normal digestive system functions, as well as eating habits. Absorbed essential and beneficial nutrients from food are used by all human organic systems to maintain their functions for the purpose of maintaining health. The immune system resists harmful agents from the environment, such as viruses and bacteria, and raises the level of its activity during infection. Such activity requires an accelerated metabolism. Increased metabolic activity requires more energy sources and specific substrates for biosynthesis of regulatory molecules and activation of cellular and biochemical elements of immune defense.

Adequate food choices and a wide range of nutrients are necessary to maintain optimal immune system function, and this is a prerequisite for an adequate response to prevent more severe clinical forms of COVID-19 disease. In the fight against the COVID-19 pandemic, little attention is paid to strengthening the natural abilities of the human body and its immune system to resist the entry of the SARS-CoV-2 virus into the human body, and prevent its replication in the cells of vital organs. There is scientific evidence that lifestyle and diet modification with nutritional interventions can strengthen the immune system and thus prevent and mitigate the pandemic spread of this disease. During the COVID-19 pandemic, it was proven that people with eating disorders, such as pathological obesity, have a higher risk of infection, as well as the occurrence of complications with a fatal outcome.

## 2. OBJECTIVE

The aim of this paper is to evaluate new findings on the impact of food, specific nutrients and eating habits on immune system function during the COVID-19 pandemic.

## 3. METHODS

The available literature was analyzed using the key words: food, immune system, COVID-19, and the results of studies that have scientific evidence (EBM) for the positive impact of food on the activity of the immune system during this disease were summarized.

## 4. RESULTS AND DISCUSSION

Food, diet and digestive function play the most important role in the overall immune response to viral infections. It has been proven that the active ingredients of food can strengthen or weaken the immune system (immunomodulation or immunosuppression). In addition to the basic physiological function in fulfilling energy needs and preserving life and health, food also has an emotional function, as well as a psychological and social one. The psychological, social and emotional function of food can directly affect the control of stress, stabilization of the emotional and psychological status of the patient, which is an important factor for maintaining a stable immune system. Some ingredients from food have a dominant effect on the digestive system, some on the circulatory system, and some on metabolic processes that take place at the cellular level. Some ingredients in direct contact destroy or inhibit various microorganisms. This action is performed by destroying the phospholipid membrane, inhibiting enzymatic reactions or acting on the genetic structure of microorganisms. Another way is to act through the immune system and various biochemical mechanisms.

Dietary supplements are often used to boost immunity. The needs for food supplements should be individualized and harmonized with the immunomodulatory properties of individual products and the assessment of the nutritional status of the consumer. Foods contain a number of immunomodulatory ingredients that have not yet been

well studied in terms of their more effective use.

Organic balanced food adapted to each person (personal diet) is the first prerequisite for creating an adequate natural defense system. Adequate immune response regardless of food choice also depends on food consumption habits, and control of all 5 functional stages of digestion. Each of these phases is controlled with the nervous system of the digestive system and the centers in the brain. Any disorder in this whole process can lead to metabolic disorders, insulin resistance, diabetes and other immune autoimmune diseases. Such disorders weaken the immune response to viral infections, so an increased incidence of COVID-19 has already been demonstrated in people with obesity, hypertension, diabetes, and autoimmune diseases. Recommendations for strengthening the immune system in the prevention of COVID-19 infection could be agreed according to the stages of digestion:

- Choosing a healthy personal diet according to basic principles of healthy nutrition.
- Eating meals at regular times.
- Chewing food long enough so the cells of the oral cavity send accurate information about the composition of the food taken.
- Drinking enough water during at meal.
- Taking enough food which is rich with fiber and prebiotics.
- To ensure healthy sleep and control of stress
- Using the amount of food for 1 meal to  $\frac{3}{4}$  stomach capacity.
- Diminish the amount of cold drinks.
- Eating lightly with thoughts of food values using principles of mindful eating and meditation
- Choosing pleasant surroundings during the meal and share it with loved ones.(family table)
- Avoiding any other activity during meals: ( e.g., using mobile phone, reading, watching tv)
- To ensure regular defecation

The first defense against the entry of the virus is at the very entrance to the respiratory and digestive system, and that is the mucous membrane of the nasal and oral cavity and eyes. The mucous membranes of these organs anatomically and functionally play very important roles in maintaining an adequate human defense system and form the initial key element in the immune response process. The first interaction between the virus and the host occurs in this part and based on this first interaction, the entire clinical course of a possible COVID-19 disease with all its complications is created. It is logical that the enemy should be stopped at the door, and that is the first line of defense. The strongest natural barrier of the first line is the healthy mucosa of the initial parts of the respiratory and digestive systems. Lashes and mucus on the surface contain substances such as lysosome and antibodies from the IgA group. There are also glycoproteins-mucins in the mucus, which can bind viruses to their structure by imitating ACE receptors and remove them outside the body in the form of mucus. These mucosal immune structures depend on the suitability of important food ingredients



such as vitamins, minerals, proteins and essential fatty acids.

Disruption in the immune function of the microbioma was registered during the COVID-19 pandemic. Studies have shown that there is a link between the digestive system and respiratory infections during COVID-19 disease. At the same time, the positive influence of prebiotics and probiotics on the course of the disease has been shown. There are studies that recommend the standard use of probiotics in the prevention and treatment of COVID-19 disease. Some probiotic cultures have the ability to act in the ACE receptor region by inhibiting virus entry into cells. A link between lung microbioma and gastrointestinal system with a synergistic immune response and prevention of bacterial lung superinfection has also been demonstrated. Adequate immune function of the intestinal and respiratory microbiome in symbiosis with the host is one of the most important conditions for preventing the onset and spread of COVID-19 disease. There is enough evidence that maintaining the normal composition of the human microbioma with the use of prebiotics from food and probiotic cultures can affect the prevention of this disease, as well as the prevention of severe respiratory complications.

There are indications that the COVID-19 pandemic also came as a result of the weakening of the immune system of the entire human race due to changes in diet that occurred in the 21<sup>st</sup> century. Until 50 years ago, humans ate mostly organic food without additives. The current global characteristic of the diet is that food is produced in conditions of polluted soil, air and water. Food is taken in supermarkets that are mostly industrially ultra-processed and with many additives, preservatives and sugars. Genetically modified food directly damages the human DNA genome and has a direct negative impact on the function of the immune system. Artificial flavors and colors, flavor enhancers, hormones and antibiotics in food deceive a person's neurotransmitters, so he/she becomes addicted to such food. The consequences of such a diet are today's pandemics of obesity, insulin resistance, metabolic syndrome, diabetes and other chronic non-communicable diseases that have greater destructive powers for human life than the SARS-CoV-2 virus itself.

There are three types of food ingredients, each of which affects the immune system in its own way. These are nutrients, biologically active ingredients and toxic, harmful components. Particularly important are biologically active components that can have immunomodulatory effects in the digestive system, bloodstream-circulation or at the level of cells and tissues. They have different mechanisms of defensive action.

The small intestine is in close and functional connections with visceral adipose tissue, which is an important endocrine and immune organ, and with the liver as a central part of all metabolic processes. The small intestine

### Immunity and probiotics

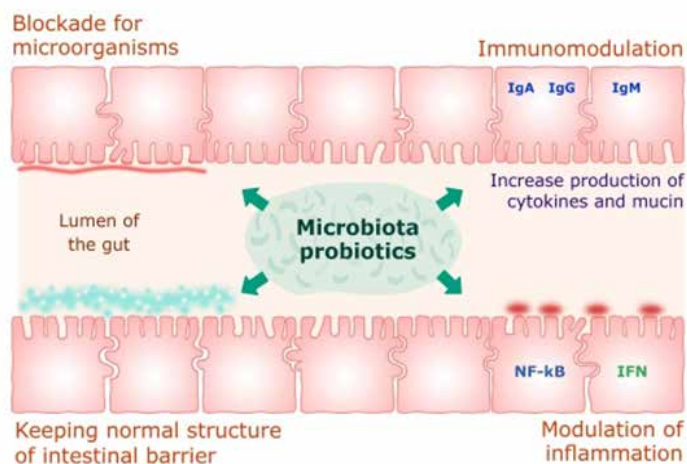


Figure 6. Immune functions of microbioma and probiotics

also has its own nerve tissue and secretes numerous neurotransmitters. Through the peripheral nervous system (n. Vagus), gastrointestinal hormones, neurotransmitters and other signaling mechanisms, there is a very complex interaction with the brain, so food and the process of digestion have a great influence on brain activity. The brain is the central immune organ and coordinates all phases of the immune response to infections. When food enters the body, and the same goes for microorganisms, the digestive system already in the mouth through receptors on the cells sends the necessary signals to the brain but also to the small intestine. The most important information about the type and quality of food and antigenic structures in the brain comes through the small intestine. The processed data in the brain activates or does not activate some of the defense immune functions. Visceral adipose tissue has a significant impact on the occurrence of pathological obesity, fatty liver, insulin resistance and type 2 diabetes, which have a negative impact on the creation of an adequate immune response. In practice, a higher incidence of COVID-19 in such diseases has been proven.

Obesity and insulin resistance is associated with the state of chronic low-grade inflammation of visceral adipose tissue with impairments of the activity B, T lymphocytes and natural killer cells. Inflammatory mediators like cytokines can be increased which produces "cytokines storm" during clinical course of COVID-19. Healthy nutrition and life styles modification in early stage of life is the best way for prevention many viral diseases.

Phytochemicals are a group of biologically active non-nutritive substances from plants. They have a functional value for the human body, acting in terms of protection against disease. For example, they can act on the immune system as immunomodulatory, adaptogenic to the endocrine system, protective for the skeletal system, antimutagenic and anticarcinogenic at the cellular level.

Immune modulation, through a nutritional strategy, has not yet been confirmed in practice but is promising

because recent studies indicate that almost all chronic noncommunicable diseases etiologically begin with a disorder of the human immune system in the digestive tract in the small intestine-visceral adipose tissue-liver axis.

Some ingredients from food can reduce the effects of inflammation. During inflammation, gene mutations can occur that can lead to disorder of immune response. The effect of antioxidants on nuclear factor  $\kappa$ B (NF- $\kappa$ B) is known here. It is a protein complex that controls DNA transcription, cytokine production and cell survival. It is involved in cellular responses to stimuli such as stress, cytokines, free radicals, heavy metals, ultraviolet radiation, oxidized LDL, and bacterial or viral antigens. Improper regulation of NF- $\kappa$ B is also associated with viral infections. Phenols and carotenoids from food, which are most often antioxidants, can affect the regulation and proper functions of the transcription process, as well as the repair of damaged DNA.

Activation of immune system for adequate response needs many nutrients, different vitamins and minerals for biosynthesis specific factors in first and second line of immune defence. Proliferation of immune cells requires synthesis DNA, many proteins and lipids. Some nutrients have important role in regulation of DNA replication. Synthesis of nucleic acid depends of present micronutrients as iron, zinc, magnesium and folate. The maturation and differentiation of immune cells depends of A and D vitamins.

Vitamin A has key role for boosting the first line of defence (barrier function) keeping normal differentiation of epithelial tissue. In the same time vitamin A increases activities of white blood cells, natural killer cells and macrophages. Deficiency of vitamin A can reduce mucus secretion, make breakdown of the mucosal barrier enabling a virus to entry in epithelial cells It is proven that vitamin A supplementation can helps to relieve clinical symptoms of pneumonia.

Vitamin C and E belong to antioxidants and make important protection against reactive oxygen damage and viral infections. Many studies showed that C vitamin has important role in prevention of severe respiratory infection. Vitamin C participates in biosynthesis of collagen and maintaining of epithelial integrity.

Many nutrients have antioxidant function. Some plant foods have vitamins, minerals and fibers which play important role in creating and maintaining of healthy immune system and healthy composition of intestinal microbioma.

Beta glucans are biologically active ingredients of cereals and mushrooms. By chemical composition these are polysaccharides containing glucose associated  $\beta$ -glycoside bonds. They are naturally found in various chemical forms in cereals (oats, barley, rye and wheat), yeasts, fungi and algae.  $\beta$ -glucans act as antioxidants and eliminate free radicals. prevent inflammation, shorten the duration of infections. Wholemeal flour of these cereals, in addition to beta glucans, contain raw fiber, which plays an important role in the process of digestion in the small intestine. Mushrooms are nutritionally valuable

food. The healing effects are given to them by macro and micro nutrients (especially selenium), and biologically active components such as beta glucans, lentinan and crestin, and ingredients with statin characteristics. As a result, mushrooms could be a very important part of functional foods as well as an important dietary supplement, especially in support of covid-19 prevention and prophylaxis. Bee products are honey, pollen, propolis, royal jelly, wax and parch as immunomodulators have strong antioxidant function.

Many studies and reviews addressed to the role of vitamin D and its metabolites on immunity during viral infection. Majority of immune cells have receptors for active form of vitamin D. There are scientific evidence for many immunoregulatory functions of vitamin D. D vitamin participates in production of antimicrobial peptide in macrophages and epithelial cells in strengthening integrity of mucosal barrier and mucosal immunity and reduction of viral replication rate. Activation of innate immune cells and regulatory T lymphocytes depends of adequate level of active form of vitamin D. For prevention, prophylaxis and treatment od COVID-19 it is necessary to use higher doses of vitamin D3. There is an inverse linear relationship between level of vitamin D and respiratory tract infections. D vitamin has important role in prevention and control clinical course of Acute respiratory distress syndrome (ARDS) and cytokines storm. Meta-analyses concluded that supplementation of vitamin D in higher doses (5000-10000i.u.) can reduce risk of infection with virus SARS-CoV-2 and prevention complication of disease.

Supplementation of vitamin D is only one of nutritional intervention to control a cytokine storm. ARDS is condition when excessive stimulation of the innate immune system leads to excessive production of proinflammatory chemokines and cytokines which make damage to all host tissue and finally severe respiratory failure. Nutrients, like vitamin C,E and D with antioxidant functions can help to control regulation of the immune respons and suppress overproduction of proinflammatory mediators.

Antiinflammatory properties have nutrient as omega-3 fatty acids.Two bioactive fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have specific anti-inflammatory function with inhibiting NF $\kappa$ B signaling. This function decreases production of inflammatory cytokines.Many clinacal studies showed that administration of omega-3 fatty acids can reduce lung inflammation, needs for ventilation and improve clinical outcomes.

The role of zinc from foods in boosting immune system during RNA viral infection were summarised in many systematic reviews.Antiinflammatory and antioxidant properties have been cleer documented. Zinc has property to inhibit RNA polymerase. SARS-CoV-2 as RNA virus use RNA polymerase for replication in human cells, so zinc decrease progression of disease.

Zinc, also, plays an important role in keeping adequate number T and B lymphocits. Supplementation of zinc is recommended as prophylaxis for COVID-19.



## 5. CONCLUSION

Currently there is no adequate treatment for COVID-19. In the fight against the COVID-19 pandemic, little attention is paid to strengthening the natural abilities of the human body and its immune system to prevent COVID-19. The immune system during viral infection increases level of its activity. Such activity requires more energy sources and specific substrates from food to activate cellular and biochemical elements of immune defense. Adequate food choices and a wide range of nutrients are necessary to maintain optimal immune system function. Organic balanced food adapted to each person (personal diet) is the first condition for creating an adequate natural defense system. Eating behavior (mindful eating) can control of stress and improve influence of nutrients on immune system response. Interaction between digestive and immune system with brain plays important role in comprehensive natural defense. Activation of immune system needs many nutrients, different vitamins and minerals for biosynthesis specific factors in first and second line of immune defense.

Vitamins A, C, D, E and mineral zinc are key factors for strengthening mucosal immunity and in production of B and T lymphocytes. Omega 3 fatty acids have anti-inflammatory and antimicrobial function and can be useful for prevention and treatment ARDS. Some components from certain foods are very valuable in maintaining a healthy immune system, such as: sea fish, berries, leafy vegetables, legumes, bee products, mushrooms and herbs.

There is evidence that this dietary approach can prevent COVID-19 disease or alleviate the clinical course, and accelerate the process of creating specific immunity.

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# The Role of 3D Power Doppler in Screening for Ovarian Cancer

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**Background:** It is clear that in developed countries more women die annually from ovarian cancer than from all other gynecologic malignancies combined. **Objective:** The aim of this article is to analyze current possibilities and propose adequate measures which can help the development of effective screening methods/assays for the early detection of epithelial ovarian cancer. **Results and Discussion:** This article updates the status of ovarian cancer screening and addresses most relevant studies published during the last five years. The developments that followed the review are best summarized in reference to the screening tests, target populations and newly published trials. The possible role of 3D ultrasound technology, especially 3D power Doppler imaging, in early and accurate detection of ovarian malignancy is discussed. We described our new ovarian cancer screening trial, which started in January 2001. Improvements in ultrasound technology such as 3D volume acquisition and 3D power Doppler imaging may have clinical utility in a more reliable identification of an abnormal ovarian vascularity and architecture. 3D volume acquisition allows for careful evaluation of the internal surfaces of cyst walls for excrescences otherwise not appreciated by 2D ultrasound. **Conclusion:** While the addition of 3D power Doppler provides a new tool for measuring the quality of ovarian tumor angiogenesis, improving accurate diagnosis of ovarian malignancies, its clinical value for the early detection of ovarian carcinoma has yet to be determined.

**Keywords:** Ovarian cancer screening, 3D and 3D power Doppler ultrasound, stage I ovarian cancer.

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## 1. INTRODUCTION

It is clear that in developed countries more women die annually from ovarian cancer than from all other gynecologic malignancies combined. For example, in the United States approximately 25 580 new cases are diagnosed each year, and 16 090 of these women will die of the disease (1). Symptoms usually do not become apparent until the tumor compresses or invades adjacent structures, ascites develops, or metastases becomes clinically evident. As a result, around 65% of women with ovarian cancer have advanced disease (stage III/IV) at diagnosis with 5-year survival rate of only 20-30%, compared with the 5-year survival of over 90% in patients with stage IA ovarian cancer, when disease is confined to the ovary (2). Given the burden of suffering associated with the de-

velopment of ovarian cancer and the clear survival gradient related to the stage of disease at diagnosis (3), there is much enthusiasm for the development of effective screening methods/assays for the early detection of epithelial ovarian cancer.

## 2. DIFFICULTIES IN OVARIAN CANCER SCREENING

The ability to detect early-stage epithelial ovarian cancer by a simple test has long been desired yet never achieved. Several aspects of ovarian cancer have led to the frustrations that have been encountered in attempts to screen for the disease (4). First, the anatomic location of the ovaries is not amenable to any direct inspection. Additionally, in contrast to cervical neoplasia, epithelial

Study	Inclusion criteria	Screening strategy	No. screened	No. of invasive epithelial ovarian cancers detected <sup>a</sup>	No. of positive screens	No. of positive screens/cancer detected <sup>b</sup>
<b>ULTRASOUND (US) APPROACH</b>						
GRAYSCALE US (LEVEL 1 SCREEN), than repeat GRAYSCALE US (LEVEL 2 SCREEN)						
van Nagell <i>et al.</i> <sup>7</sup>	Age > 50 years and postmenopausal or > 30 with positive family history	TVS Annual screens Mean 4 screens/women	14469	11 (6) 5 stage I	180	16,4
Hayashi <i>et al.</i> <sup>8</sup>	Age > 50 years	TVS	23451	3 (3)	258	<sup>c</sup>
Tabor <i>et al.</i> <sup>9</sup>	Aged 46-65 years	TVS	435	0	9	-
Campbell <i>et al.</i> <sup>10</sup>	Age > 45 years or with positive family history (4%)	TAS 3 screens at 18 monthly intervals	5479	2 (3) 2 stage I	326	163
Goswamy <i>et al.</i> <sup>11</sup>	Age 39-78 Postmenopausal	TAS	1084	1 1 stage I	not precised	-
GRAYSCALE US and CDI (LEVEL 1 SCREEN)						
Vuento <i>et al.</i> <sup>12</sup>	Aged 56-61 years	TVS and CDI	1364	(1)	5	-
Kurjak <i>et al.</i> <sup>13</sup>	Aged 40-71 years	TVS and CDI	5013	4 4 stage I	38	9,5
Schulman <i>et al.</i> <sup>14</sup>	Age > 40 years or > 30 with positive family history	TVS and CDI	2117	1	18	18
GRAYSCALE US (LEVEL 1 SCREEN) and other tests (LEVEL 2 SCREEN)						
Sato <i>et al.</i> <sup>15</sup>	Age > 30 years	TVS then tumour markers if TVS +, CT and MRI if all previous +	51550	16 (6) 12 stage I	324	20,3
Parkes <i>et al.</i> <sup>16</sup>	Aged 50-64	TVS then CDI if TVS +	2953	1 1 stage I	15	15
Holbert <i>et al.</i> <sup>17</sup>	Postmenopausal Aged 30-89 years	TVS then CA 125 if TVS +	478	1 1 stage I	33 <sup>d</sup>	-
TOTAL <sup>e</sup>				37 (16) 23 stage I	880	23,8

Table 1. Prospective ovarian cancer screening studies using ultrasound as the primary test in the general population. TAS = transabdominal ultrasound; TVS = transvaginal ultrasound; CDI = Color Doppler imaging, <sup>a</sup>The borderline/granulosa tumours detected are shown in parenthesis. <sup>b</sup>Only invasive epithelial ovarian cancers included. <sup>c</sup>Only 95 women consented to surgery and there are no follow up details on the remaining. <sup>d</sup>Only 11 of these women underwent surgery., <sup>e</sup>Studies used TAS are excluded.

ovarian cancers lack any defined precursor lesion and have a poorly defined natural history. The time required for localized disease to progress to disseminated disease is unclear; therefore the appropriate interval at which to pursue screening is at this point chosen arbitrarily. Other impediments to screening relate to the low prevalence of ovarian cancer in the general population. Therefore, a specificity of 99.6% is required to achieve a positive predictive value of 10% i.e. to limit the number of unnecessary surgical procedures to 10 for each case of cancer detected (5). A specificity lower than this is likely to be unacceptable in this population, although may be acceptable to those with a positive family history of breast or ovarian cancer.

### 3. ATTEMPTS TO SCREEN – SOME LESSONS LEARNED

During the last decade, large prospective studies of screening for ovarian cancer have been performed (6). Two distinct strategies have emerged, one based on ultrasound as the primary test, and the other involving the serum tumor marker CA 125 for primary screening with ultrasound as the secondary test (multimodal screening). Tables 1 and 2 summarize the prospective ovarian cancer screening studies in the general population (7-22). If we

exclude those which used transabdominal ultrasound, an abandoned screening strategy due to unacceptably high rate of false positive results, several important lessons can be learned for forthcoming trials.

As seen in Tables 1 and 2, the data suggests that sequential multimodal screening has greater specificity and positive predictive value compared to strategies based on transvaginal ultrasound alone. For each case of ovarian cancer detected, five women underwent surgery in the multimodal studies compared to 24 women in the studies using ultrasound alone. However, transvaginal ultrasound as a first line test may offer higher sensitivity for early stage disease given that 23/37 (62,2%) cancers detected using ultrasound alone were stage I, compared to 8/19 (42,1%) cancers detected by the multimodal strategy. An ultrasound-based strategy may have a greater impact on ovarian cancer mortality, albeit at a higher price in terms of surgical intervention for false positive results.

This article updates the status of ovarian cancer screening and addresses most relevant studies published during the last five years. The developments that followed the review are best summarized in reference to the screening tests, target populations and newly published trials. The possible role of 3D ultrasound technology, especially 3D power Doppler imaging, in early and accurate

Study	Inclusion criteria	Screening strategy	No. screened	No. of invsive epithelial ovarian cancers detected	No. of positives screens	No. of positive screens/cancer detected
<b>CA 125 ONLY</b>						
Einhorn <i>et al.</i> <sup>18</sup>	Age > 40 years	Serum CA 125	5550	6 2 stage I	175	29,2
<b>MULTIMODAL APPROACH</b>						
CA 125 (LEVEL 1 SCREEN), then GRAYSCALE US (LEVEL 2 SCREEN)						
Jacobs <i>et al.</i> <sup>19</sup>	Age > 45 years Postmenopausal	RCT Serum CA 125 TAS/TVS, if CA 125 † 3 annual screens	10958	6 3 stage I	29	4,8
Jacobs <i>et al.</i> <sup>20</sup>	Age > 45 years Postmenopausal	Serum CA 125 TAS, if CA 125 †	22000	11 4 stage I	41	3,7
Adonakis <i>et al.</i> <sup>21</sup>	Age > 45 years	Serum CA 125 TVS, if CA 125 †	2000	1 (1) 1 stage I	15	15
Grover <i>et al.</i> <sup>22</sup>	Age > 40 years or with positive family history (3%)	Serum CA 125 TAS/TVS, if CA 125 † 3 screens	2550	1	16	16
TOTAL <sup>a</sup>				19 (1) 8 stage I	101	5,3

RCT = randomised controlled trial  
<sup>a</sup>Only multimodal approach studies included.

Table 2. Prospective ovarian cancer screening studies using serum CA 125 as the primary test in the general population

detection of ovarian malignancy is discussed. Finally, we describe our new ovarian cancer screening trial, which started in January 2001.

#### 4. SCREENING TESTS

Screening for ovarian cancer has been based on strategies using serum tumour markers or transvaginal ultrasound images of the ovaries.

##### Serum tumor markers

In epithelial ovarian cancer, a number of tumour markers have been identified. Serum CA 125 continues to be the tumour marker most extensively used in ovarian cancer screening (23). Although CA 125 is elevated (>35 U/ml) in more than 80% of patients with epithelial ovarian cancer it is only 25% sensitive for early stage disease (24). Indeed, its value as an initial screening tool is limited since picking up stage III disease at an earlier time may not alter outcome. To improve further the performance of CA 125 as a screening tool, an algorithm incorporating age, rate of change of CA 125 and absolute levels to calculate an individual's risk of ovarian cancer has been described (25). This increases the sensitivity of CA 125 in comparison with a single cutoff value, because women with normal but rising levels are identified as being at increased risk. This approach is an integral part of the multimodal screening strategy adopted in the St Bartholomew's Hospital newest randomized control trial (26).

Another limitation of serum CA 125 represents that it is not specific for ovarian carcinoma because it can be elevated in many benign conditions such as endometriosis, uterine fibroids, pelvic inflammatory disease, ascites or pleural effusion (27). It is now known that the CA 125 antigen carries two major antigenic domains classified as A (the domain binding monoclonal antibody OC125) and B (the domain binding monoclonal antibody M11). New gen-

An eligible woman must be over 25 years of age and a first degree relative of an affected member of an "at risk" family. At risk families are defined by the following criteria:

- 1 Two or more first degree relatives<sup>a</sup> with ovarian cancer.
- 2 One first degree relative with ovarian cancer and one first degree relative with breast cancer diagnosed under 50 years of age.
- 3 One first degree relative with ovarian cancer and two first or second degree relatives<sup>b</sup> with breast cancer diagnosed under 60 years of age.
- 4 An affected individual with one of the known ovarian cancer predisposing genes.
- 5 Three first degree relatives with colorectal cancer with at least one diagnosed before the age of 50 years and at least one first degree relative with ovarian cancer.

<sup>a</sup>A first degree female relative is mother, sister or daughter.

<sup>b</sup>A second degree female relative is grandmother, grand-daughter, aunt or niece.

Table 3. Eligibility criteria for the UK National Familial Ovarian Cancer Screening Study<sup>39</sup>

eration assays, combining monoclonal antibodies to the two distinct regions of the molecule, have been shown to have improved specificity for the detection of early ovarian cancer (28).

Lysophosphatidic acid (LPA), a bioactive phospholipid with mitogenic and growth factor-like activities (29), is a novel tumor marker that holds promise in ovarian cancer screening. In a small pilot series plasma LPA levels were elevated in 9 out of 10 patients with stage I ovarian cancer, 24 of 24 patients with stage II, III and IV ovarian cancer, and all 14 patients with recurrent ovarian cancer (30). In comparison, among a subset of patients with ovarian



Technique	No. of detected cancers (%)	No. of missed cancers (%)
2D US	30 (69,8)	13 (30,2)
2D US/TVCD <sup>a</sup>	37 (86,0)	6 (14,0)
3D US	32 (74,4)	11 (25,6)
3D PD	41 (95,3)	2 (4,7)
3D US/3D PD <sup>b</sup>	42 (97,7)	1 (2,3)

<sup>a</sup>Combined 2D morphology and color Doppler score.

<sup>b</sup>Combined 3D morphology and power Doppler score.

**Table 4. Diagnostic accuracy of four different techniques [two-dimensional (2D) transvaginal ultrasound (US), 2D transvaginal color Doppler (TVCD), three-dimensional (3D) US, and 3D power Doppler (3D PD)] in preoperative sonographic assessment of 43 patients with suspected stage I ovarian cancer<sup>53</sup>**

cancer, only 28 out of 47 had elevated CA 125 levels, including 2 of 9 patients with stage I disease. Larger studies on the use of LPA in primary screening – perhaps in combination with other procedures, such as transvaginal ultrasound – are essential for earlier detection and improved outcome for patients with ovarian cancer (31).

#### Transvaginal ultrasound

Transvaginal ultrasound is used in most screening strategies either as the sole screening modality or as a secondary test after primary screening with serum CA 125 (multimodal screening). As data regarding outcome accumulate with long-term follow up of the participants of the early screening trials, it has been possible to define further risk of ovarian cancer associated with various ultrasound findings.

Particular results of the largest ultrasound-based ovarian cancer screening project from University of Kentucky might have a definitive impact on design of future ovarian cancer screening trials in the general population (32). van Nagell et al. established that unilocular ovarian cysts less than 10 cm in diameter, found in 256 out of 7705 (3,3%) asymptomatic women aged more than 50 years, are associated with a minimal risk for ovarian cancer because there were no cases of ovarian carcinoma during a 5-year follow up period (33). In contrast, 7 out of the 250 women in the same study with complex cystic ovarian tumors, including wall abnormalities or solid areas, had ovarian carcinoma suggesting that this morphologic appearances are associated with a significant risk for malignancy.

In many screening algorithms, volume cut-offs are used in addition to morphology characteristics to identify women for intensive surveillance. Recently, based on the data on 58 673 observations of ovarian volume, authors from Kentucky concluded that the upper limit of normal for ovarian volume is 20 cm<sup>3</sup> in premenopausal women and 10 cm<sup>3</sup> in postmenopausal women (34). Such data are invaluable in determining optimal strategies for operative intervention in screening trials.

Postmenopausal women from the general population

with an elevated serum CA 125 level but normal ovarian morphology on ultrasound were found to have a cumulative risk of ovarian cancer during a median follow up of 6,8 years, of 0,15%, which was similar to 0,22% of the entire population of 22 000 women (35). In contrast, those with an elevated serum CA 125 level and abnormal ovarian morphology on ultrasound had a significantly increased cumulative risk of 24%. The use of ovarian morphology to interpret pelvic ultrasound may increase sensitivity, and use of complex ovarian morphology may increase the positive predictive value of a multimodal screening strategy (36).

## 5. TARGET POPULATIONS

Participants for ovarian cancer screening trials are recruited from general and high-risk populations on the basis of risk factors for the disease.

### General population

#### Age and menopausal status

The bulk of ovarian cancers occur in the general population, and age greater than 50 years and postmenopausal status have been used to define those eligible for screening. According to the recent FIGO report (2), appearance of ovarian cancer is most common among women in early postmenopausal, at average age of 54 years. Law et al (37) used national statistics to determine the number of years of life lost through deaths from a particular cancer at each age. They concluded that screening would be most effective (i.e. associated with the largest number of years of life saved per person screened) if done 5 years before loss of life peaked. The peak occurred in ovarian cancer during the age range 55-59 years, and the authors' argument provides further justification for using 50 years as the cutoff to commence population screening.

### High-risk population

#### Family history and/or genetic predisposition

Approximately 5-10% of ovarian cancers are inherited. Mutations in *BRCA1* and *BRCA2* genes account for about 75% of families with a highly penetrant dominantly inherited breast or ovarian cancer family history. Recent estimates of the lifetime risk for ovarian cancer in women harboring a *BRCA1* mutation are 40%–60% (38). Various studies have put forward schemes for stratifying women into different risk categories of risk for breast and ovarian cancer by virtue of a family history, genetic predisposition or both. Pharoah et al. (39) reviewed the relevance of family history in defining the target population for familial ovarian cancer screening, and propose the adoption of a unified management strategy based on eligibility criteria from UK National Familial Ovarian Cancer Screening Study (Table 3). A survey by Vasen et al. (40) of the European Familial Breast Cancer Collaborative Group found that the following high-risk populations were offered ovarian cancer screening: *BRCA1* and *BRCA2* mutation carriers; members of breast/ovarian cancer families; and, in some centers, members of «breast cancer only» families with an early onset of breast cancer.



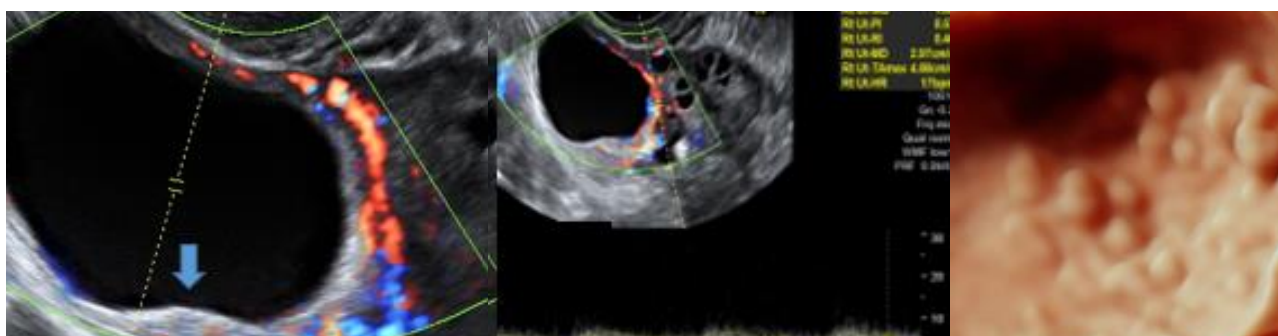


Figure 1. Ultrasound images of a serous borderline ovarian tumor: Unilocular cyst, dimension >5cm, peripheral vascularization Ri = 0,40, irregularity of cyst wall ( arrow),(a,b); On 3D HDI – microcystic area of the same region is clearly visible (c)

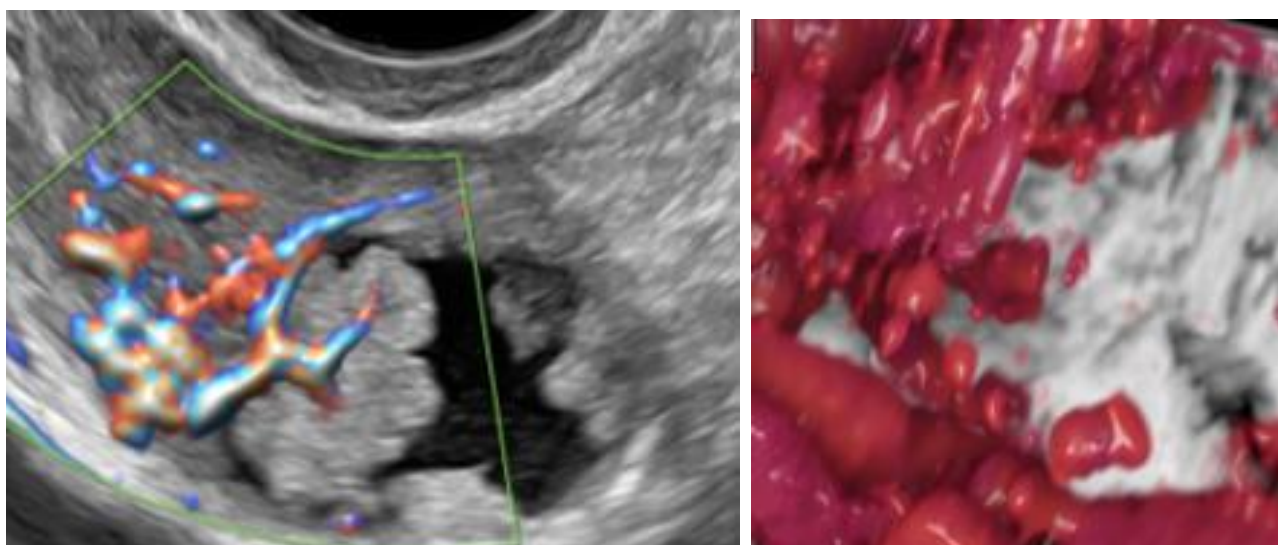
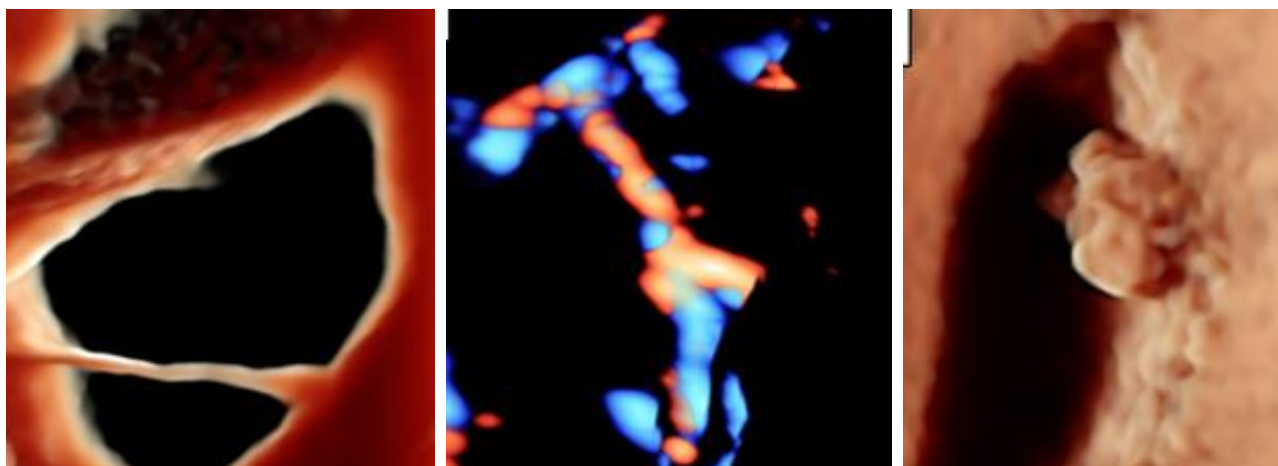


Figure 2. Vascularized septa (a,b) and papilla (c,d,e): a signs of malignancy in cyst adenomas

## 6. OVARIAN CANCER SCREENING TRIALS

Clinical trials of ovarian cancer screening have involved strategies using ultrasound alone, and a multi-modal approach with CA 125 as a primary test and ultrasound as a secondary test. Prospective studies have involved both the general and high-risk populations.

### General population

#### Ultrasound screening

In the most recent update from the University of Kentucky trial, the results of annual transvaginal ultrasound screening performed on 14 469 asymptomatic women aged 50 years or more and women aged 25 years or more

with a family history of ovarian cancer were reported (7). 180 patients with persisting transvaginal abnormalities were subjected to a surgical intervention. 17 primary ovarian cancers were detected of which 11 were epithelial ovarian cancers (EOC), three were granulosa cell tumours, and three were borderline tumours. Of the EOC, 5 were stage I, 3 were stage II and 3 were stage III. In this study transvaginal ultrasound (TV US) as a screening modality was associated with sensitivity of 81%, specificity of 98,9%, positive predictive value of 9,4%, and negative predictive value of 99,97% for detection of all primary ovarian cancers. The survival of patients with EOC in the

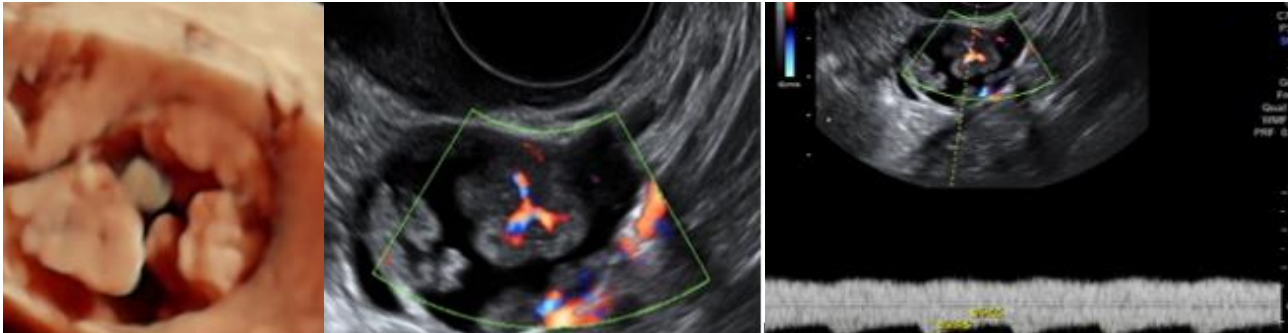


Figure 3. A case of young women 28 years old, primipara; 2D/3D and color Doppler ultrasound: Unilocular-solid appearance of the cyst; >4 papilla; color score 3; central vascularization of papilla RI <0,40 (a-c). Ph: Cystadenoma border line ovarian malignancy.

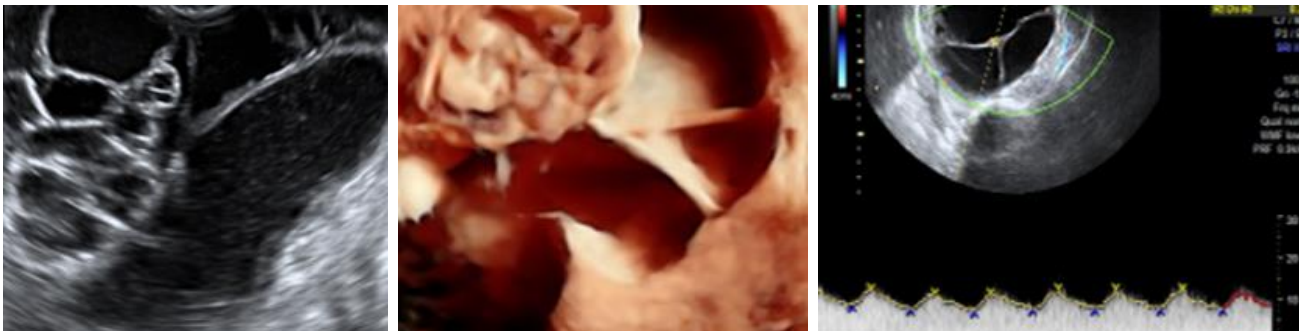


Figure 4. A case of women with Hugh tumor formation at post menopause: 2D/3D and color Doppler ultrasound: Multilocular-solid cyst, irregular cyst wall, dimension > 15 cm; multiple vascularized septa Ri<0,40 PH: Cystadenoma border line

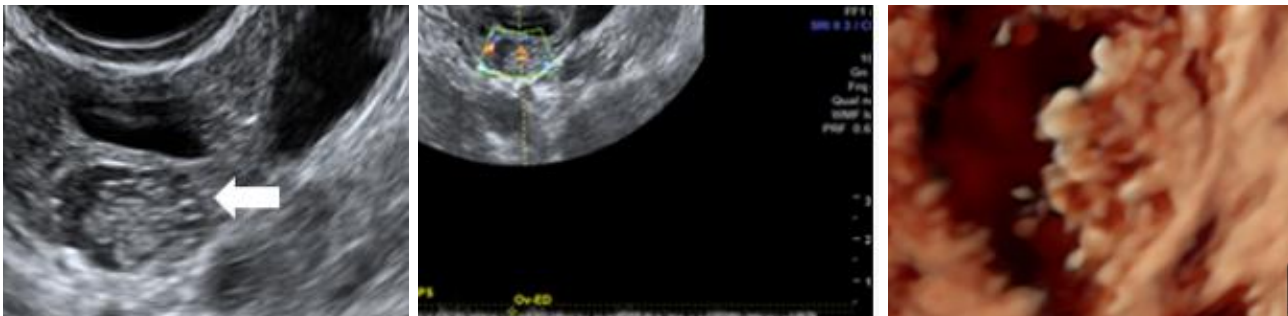


Figure 5. Micro cysts on a papilla – BOT

annually screened population was 92,9% at 2 years and 83,6% at 5 years. What is encouraging about these results is that annual TV US screening appeared to achieve the primary goal of earlier detection of disease, which translates into a reduction in mortality associated with ovarian carcinoma. On the other hand, data from this study suggested that in certain cases, length of time required for ovarian cancer to progress from a localized sonographically detectable tumor to widespread regional disease is quite short. In four patients in the false-negative group disease progression from sonographically normal ovaries to stage II or III ovarian cancer occurred in less than 12 months. Authors stated that in future screening algorithms, consideration should be given to a screening interval of 6 months.

In the recently published Japanese ovarian cancer screening trial, 51 550 women aged 30 years or more attending for annual cervical screening underwent TV US screening for ovarian cancer (15). 324 women with

masses of more than 60 mm in diameter or with a mixed echo pattern or persistently raised tumour markers underwent laparotomy. Twenty-two primary ovarian tumours and two metastatic tumours were detected. Of the 22 primary tumours, 16 were EOCs, four were borderline malignancies and two were germ cell tumours. 11 (68,7%) of the EOCs were stage I, with tumour markers positive in 5 (45,4%) of the 11 cases. The positive predictive value of the screening strategy was 4,9%; in other words 20 operations were undertaken for each detected case of ovarian cancer. As no follow-up data was reported on any of the trial participants, it is difficult to assess sensitivity of the screening strategy. Prior to the onset of the screening, the authors note that only 29,7% of 35 cancers diagnosed in the department were stage I while after the trial was initiated 58,8% of 85 ovarian cancers treated were stage I.

#### Multimodal screening

One of the most active group in screening for ovarian malignancy leaded by Jacobs, recently reported the re-



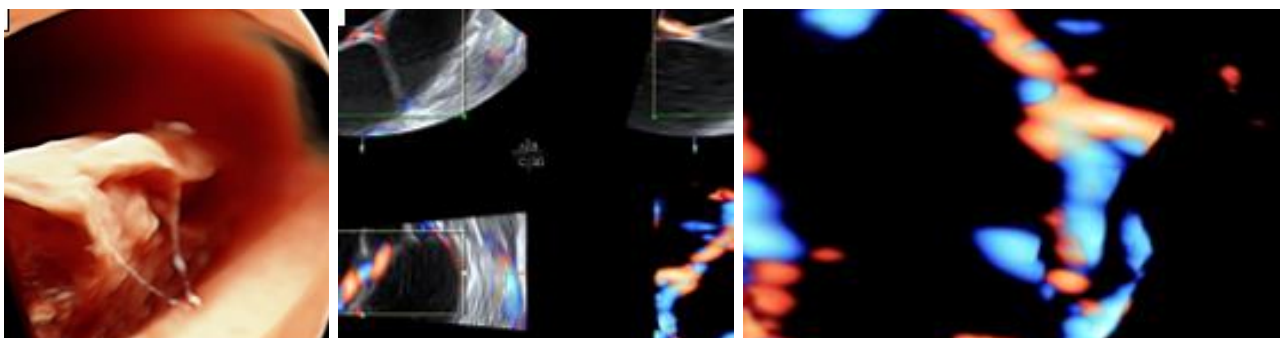


Figure 6. Differential diagnosis between hemorrhagic corpus luteum (a) and serous cystadenocarcinoma of the ovaries (b,c). Intracavitary septa of corpus luteum is never vascularized and tiny, different to carcinoma septa that is thicker and vascularized.

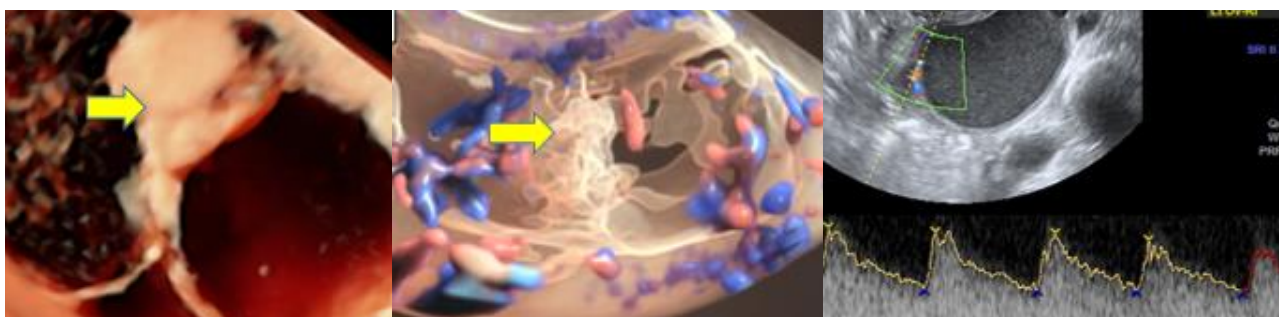


Figure 7. 2D/3D ultrasound image of endometrioma: Hiperefogenic bulk on the wall of the cyst(a), no vascularization on angio mode(b). Multilocular appearance of the cyst. The ground glass echogenicity and hyperechoic bulk , Vascularization on the wall of the cyst – Ri.0.54(c)

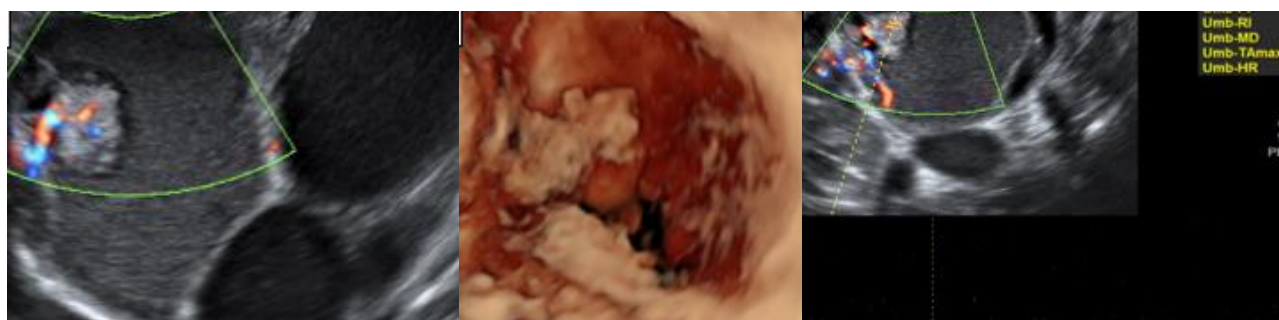


Figure 8. 2D/3D Color Doppler ultrasonography of malignant alteration of endometriosis. Papillary projection and low Ri on papillary blood vessel.(a,b, c,)

sults of the first completed randomized trial of ovarian cancer screening (19). This study randomized asymptomatic postmenopausal women aged 45 years or older to no screening (n=10 977) or to annual multimodal screening for 3 years (n=10 958). In the screening group 29 women with raised CA 125 values and abnormal ultrasound findings were referred for surgical investigation. All 6 ovarian cancers detected were EOCs; 3 were stage I and 3 were stage III. The authors found a high positive predictive value of 20,7% with this schema and were encouraged by a longer median survival (72,9 months) in women with ovarian cancer in the screened group when compared to the control group (41,8 months). The mortality rates, however, were not significantly different between the groups. The authors concluded that the results do not justify ovarian cancer screening in the general population but do support the need for a larger randomized trial that is powered to assess the impact of screening on mortality.

**High-risk population**

For women with a known germline mutations or with a family history suggesting a significant possibility of a

genetic predisposition to ovarian cancer, the appropriate screening strategy remains undefined. In recent studies, most authors advocate multimodality screening using TV US and serum CA 125 in patients who elect to delay or decline prophylactic oophorectomy. However, there is no consensus as to the appropriate interval for screening.

Karlan et al. reported the results of an ovarian cancer screening program launched in 1991, involving 1261 women aged over 35 years with a family history of ovarian, breast, colon or endometrial carcinoma, or a personal history of breast cancer (41). Screening with TV US, colour Doppler imaging and CA 125 was initially performed biannually until 1995, and annually thereafter. Two tumours of low malignant potential, one stage I EOC and 7 cases of primary peritoneal serous papillary carcinoma were diagnosed. Ultrasound abnormalities triggered surgical exploration in all three cases of ovarian disease. In 2 out of 7 cases, elevated levels of CA 125 were the harbinger of peritoneal serous papillary carcinoma, in two abnormal ultrasound findings prompted diagnosis, and three developed interval cancers 5, 6 and 16

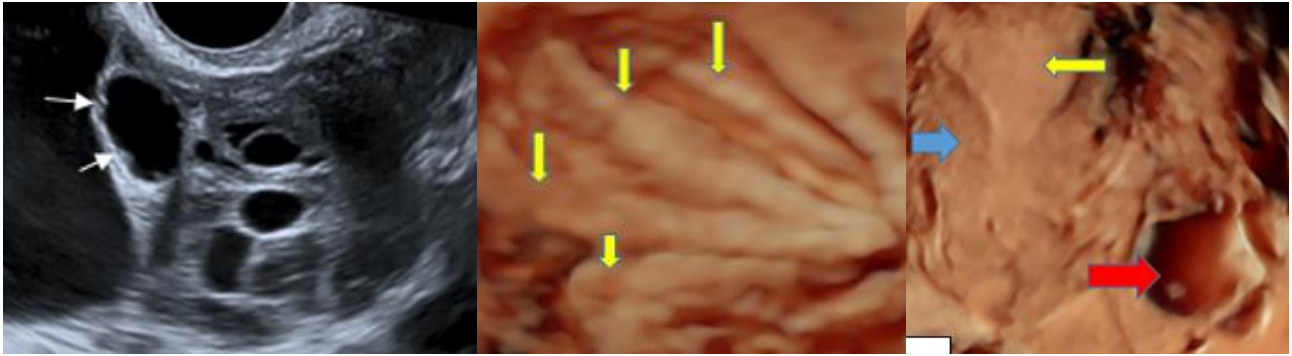


Figure 9. 2D/3D vaginal ultrasound of Chronic Hydrosalpinx: The 'beads-on-a-string' sign: hyperechoic mural nodules on the cross-section of the tube (a) (arrows); on the longitudinal section on the wall, tiny projections protrude into the lumen (arrows), the degenerated and flattened endosalpingeal fold remnants (b); 3D rendering of uterus (blue arrow), endometrium (yellow arrow), hydro salpinx (red arrow)(c)

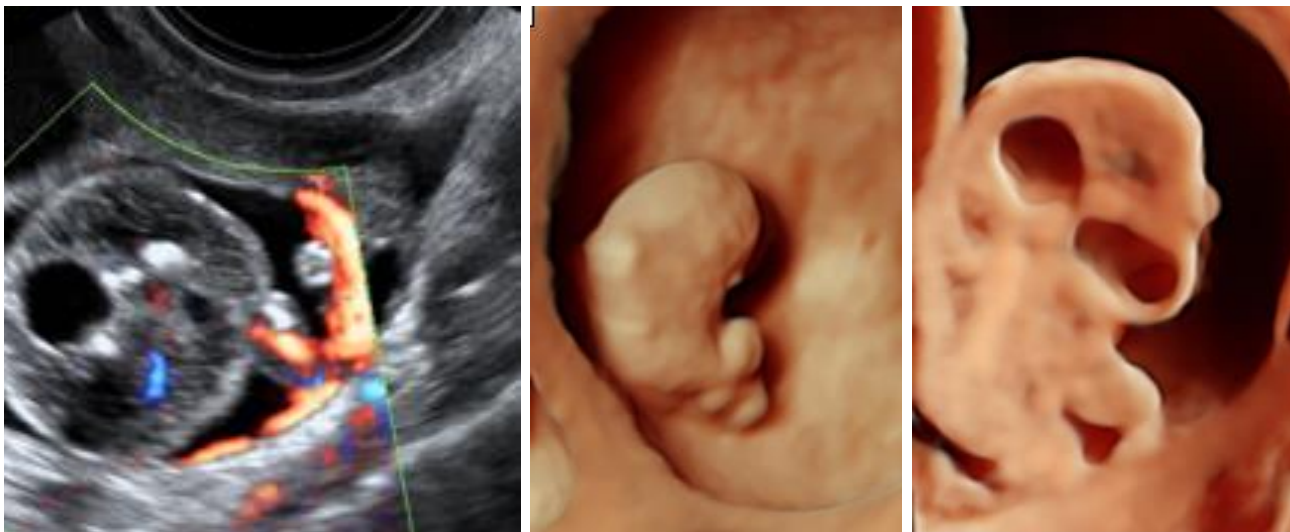


Figure 10. 2D/3D Ultrasound of Immature Teratoma: Unilocular cystic formation with thin capsule, the intracavitary space of cyst was with hypoechogenic pattern (fluid) and one solid structure with hyperechoic pattern and few small rounds hypoechogenic (microcystic) structure (a,b); Note the very fast growth of the intracavitary solid projection in the tumor approximately 3 weeks after first ultrasound, increase in size several times(c)

months after screening. At least three of the patients with primary peritoneal cancer carried mutations of the BRCA1 gene. Multifocal peritoneal serous papillary carcinoma may be a phenotypic variant of familial ovarian cancer, and screening strategies for these women cannot rely on ultrasound and CA 125 testing to detect early disease.

#### OVARIAN CANCER – THE ROLE OF 3D ULTRASOUND AND 3D POWER DOPPLER IMAGING

Improvements in ultrasound technology such as 3D volume acquisition and 3D power Doppler imaging may have clinical utility in a more reliable identification of an abnormal ovarian vascularity and architecture. 3D volume acquisition allows for careful evaluation of the internal surfaces of cyst walls for excrescences otherwise not appreciated by 2D ultrasound (42,43). While the addition of 3D power Doppler provides a new tool for measuring the quality of ovarian tumour angiogenesis (44), improving accurate diagnosis of ovarian malignancies (45), its clinical value for the early detection of ovarian carcinoma has yet to be determined.

##### What does 3D ultrasound add?

In the pioneer work, Bonilla-Musoles et al (42) tried to

determine whether 3D ultrasound may offer advantages over 2D ultrasound as a screening tool for the evaluation of ovarian lesions. Seventy-six women with ovarian masses first detected with 2D ultrasound were then evaluated with 3D ultrasound. The 3D sonographic criteria used for diagnosing ovarian malignancy were based on the morphologic scoring system for 2D transvaginal ultrasound examinations proposed by different authors (46-49). A score greater than 4 caused suspicion of a malignant ovarian mass (49). The images were dissected in the three perpendicular planes, and the areas indicative of malignancy, as suggested by 2D ultrasonography, were determined to be either negative or positive and confirmatory. Five lesions observed on 2D ultrasound were suspected to be malignant. 3D sonography identified four of these lesions as malignant. The remaining one suspected to be malignant on 2D ultrasound was diagnosed as endometriosis with 3D sonography. One additional ovarian carcinoma was diagnosed by 3D scanning. Two of the malignant lesions were FIGO stage IA. The other tumors were FIGO stages IC, IIC, and IIIB, respectively. Authors stated that observation of papillary projections (especially those less than 3 mm), characteristics of cystic

walls, and the extent of capsular infiltration was superior with 3D ultrasound in comparison to conventional 2D sonographic measurements, as was the calculation of ovarian tumor volume. They also pointed out that eventually 3D ultrasound imaging will allow diagnosis of ovarian malignancy at an earlier stage than is possible with currently established diagnostic techniques.

Volumes of irregular structures are measured precisely using 3D USG. Moreover, it is better at demonstrating septae, cyst wall irregularities, and papillary projections (50). These qualities help to understand the exact morphology of the adnexal mass. A meta-analysis by Dodge et al. reported an overall sensitivity of 93.5 % and specificity of 91.5 % for 3D gray-scale USG for identifying suspicious adnexal masses (51).

**Advantages of 3D power Doppler imaging**

There are two potential advantages of this new imaging modality: more accurate diagnosis of ovarian cancer and possible detection of stage I disease.

Illustrative examples are given in Figures 1-10.

*More accurate diagnosis of ovarian cancer*

To determine whether three-dimensional power Doppler can improve the ability to differentiate benign from malignant ovarian masses, Kurjak et al. (52) performed transvaginal color Doppler and 3D power Doppler analysis on 120 patients with ovarian lesions. As a result, in each of 11 ovarian malignancies preoperative diagnosis by 3D power Doppler was confirmed by histopathology. Transvaginal color Doppler missed 1 case of serous cystadenocarcinoma, while 3 benign lesions (dermoid cyst, ovarian fibroma, and ovarian cystadenofibroma) were considered false positive. In one case of cystadenofibroma, 3D power Doppler finding were falsely positive. Authors emphasized that irregular and randomly dispersed vessels with complex branching, depicted by 3D power Doppler imaging, were indicative for ovarian malignancy. Such qualitative analysis of the tumor vascularity architecture had a sensitivity, specificity, and positive predictive value (PPV) of 100, 99,08, and 91,67% in detection of ovarian malignancy, respectively.

In the recently published study by Cohen et al (53), 71 women with a known complex pelvic mass were referred for a preoperative ultrasound evaluation with both two-dimensional grayscale and 3D power Doppler ultrasound. All the women underwent surgical exploration, and 14 had ovarian cancer. Two-dimensional grayscale ultrasound identified 40 masses as suspicious for cancer, including all 14 malignancies, yielding a sensitivity, specificity, and PPV of 100, 54, and 35%, respectively. However, evaluation with 3D power Doppler identified only 28 cases as suspicious (including all cancers), resulting in

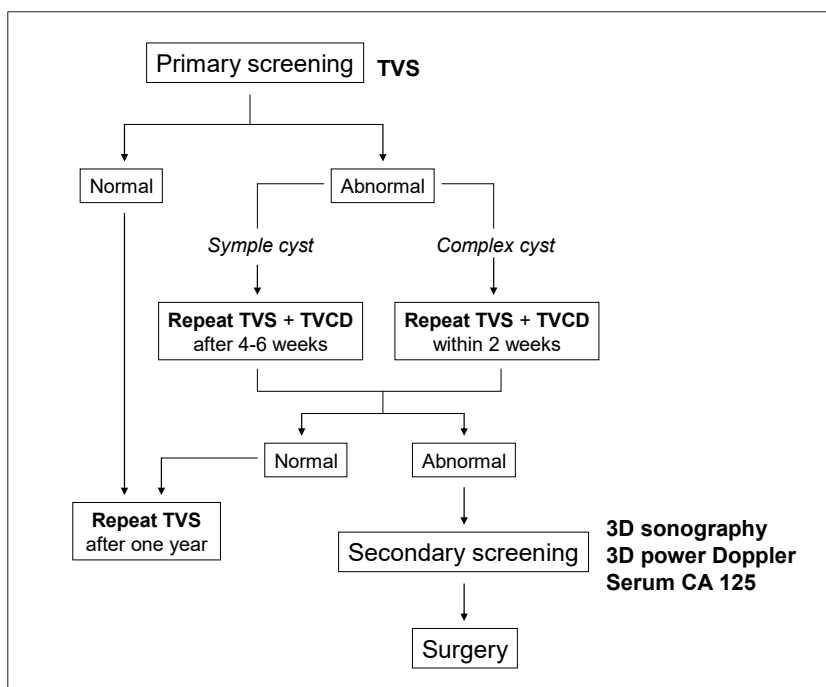


Figure 11. Screening algorithm of the Zagreb Ovarian Cancer Screening Trial

a sensitivity, specificity, and PPV of 100, 75, and 50%, respectively. Despite all malignancies were correctly identified by both 2D and 3D imaging, the specificity was significantly improved with the addition of 3D power Doppler. This improved diagnostic accuracy, authors stated, may promote improved patient care by separating complex benign masses from ovarian cancer, therefore facilitating appropriate physician referral.

Kupesic and Kurjak very recently reported on the use of contrast-enhanced, 3D power Doppler ultrasound in the differentiation of benign and malignant adnexal lesions (54). A total of 45 patients with complex adnexal lesions of uncertain malignancy at transvaginal B mode and/or color Doppler ultrasound were prospectively evaluated with 3D power Doppler before and after injection of contrast agent. There were 12 cases of ovarian malignancy and 33 benign adnexal lesions. Of the 12 ovarian cancers, seven (58,3%) showed vascular distribution suggestive of malignancy at nonenhanced 3D power Doppler imaging. After injection of contrast agent, a penetrating vascular pattern and/or a mixed penetrating and peripheral pattern were detected in all cases of ovarian malignancy. One cystadenofibroma demonstrated penetrating vessels at initial scan, whereas two benign lesions (fibroma and cystadenofibroma) were misdiagnosed as malignant at contrast-enhanced 3D power Doppler. The use of a contrast agent with 3D power Doppler showed diagnostic efficiency (95,6%) that was superior to that of nonenhanced 3D power Doppler ultrasound. Authors concluded that contrast-enhanced 3D power Doppler imaging might more precisely discriminate benign from malignant complex adnexal masses.

*The detection of stage I disease*

Preliminary results of our team showed that 3D power



Doppler ultrasound can enhance and facilitate morphologic and functional evaluation of an early stage ovarian cancer (55). Five-year retrospective analysis was performed on the data from 43 referred patients with suspected stage I ovarian cancer subsequently confirmed by histopathology. All the patients were preoperatively evaluated by four complementary sonographic methods: 2D transvaginal grayscale, 2D transvaginal color Doppler, 3D ultrasound and 3D power Doppler, during the week prior to surgery. Our results clearly demonstrated the significant impact of 3D power Doppler imaging on the accurate detection of stage I ovarian cancer. By using combined 3D morphology and vascular score indexing, we reached diagnostic accuracy of 97,7% in preoperative sonographic assessment of the suspected lesions (Table 4). These finding justify implementation of 3D ultrasound with power Doppler facilities in ovarian cancer screening programs, especially as a secondary screening tool.

## 7. ZAGREB OVARIAN CANCER SCREENING TRIAL

Following our first attempt to screen for ovarian cancer (13), in January 2001 we initiated the new ovarian cancer screening trial at our Department, based on new diagnostic tools now used routinely by us.

### Subjects and methods

During a five-year period, approximately 10 000 asymptomatic postmenopausal women  $\geq 50$  years and women  $\geq 25$  years of age with a positive family history of ovarian and/or breast cancer in at least one primary or secondary relative will be offered to participate in the trial. The screening algorithm is illustrated in Figure 11.

Primary screening include annual transvaginal ultrasound (TV US) and transvaginal color Doppler (TVCD) examination/scoring according to the sonographic and color Doppler criteria established previously by our team (56). Women with an abnormal first level screen undergo a repeat TV US sonogram, with addition of TVCD, depending on tumor morphologic appearance: in the case of simple ovarian cyst for 4-6 weeks, while if complex ovarian cyst persists within 2 weeks. In patients with a persistently abnormal screen, secondary screening will be considered necessary, including 3D ultrasound and 3D power Doppler imaging, with a serum CA 125 determination. For an examination/scoring, three-dimensional sonographic and power Doppler criteria established in our previous study are used (56). In the case of an abnormal second level screen, surgical removal of the ovarian tumor and pathological examination is recommended.

### Illustrative case

Here we present an illustrative case of successfully detected stage IA ovarian cancer in an asymptomatic, 57-year-old postmenopausal patient included in our new screening trial. She was well educated and concerned about family history of cancer, because her mother and mother's sister had breast cancer. Besides regular mammography and gynecological check-ups, patient decided to perform gynecological ultrasound in an outpatient

clinic, for the first time in her life.

Transvaginal grayscale sonography, performed by her primary care gynecologist, revealed a complex cystic-solid tumor of the right ovary, measuring 8 cm in diameter, with noticeable solid component and thick, irregular septum. Regarding ovarian morphology indicative for malignancy, she was immediately directed to our department for further ultrasound evaluation.

We confirmed previous TV US finding, and 2D power Doppler imaging showed highly vascularized zone within the septum.

Another step represented transvaginal color Doppler analysis of tumoral blood flow which revealed RI of 0,40 as the lowest value.

According to our color Doppler criteria, this finding was indicative for a malignant ovarian lesion.

The vascular pattern obtained by further analysis with 3D power Doppler imaging clearly depicted disorganized, randomly dispersed vessels with irregular branching in solid part of the tumor, strongly associated with ovarian malignancy. Typical features of malignant vascular tree like microaneurysms, arteriovenous shunts, tumoral lakes, disproportioned calibration, elongation, coiling and dichomatous branching can all be best appreciated by 3D power doppler. Increased vascular density is also an important feature that raises the doubt of malignancy. Density of the vessels was found to be a single best vascular predictor of malignancy (57).

As B mode ultrasound with doppler only assesses one or two or a few vessels, it is 3D ultrasound that can demonstrate the global vascularity and compare the vascular density of benign and malignant lesions subjectively. A number of studies examined the suspicious areas in adnexal masses and found that 3D PD indices were significantly higher in those that are malignant (58-61).

3D PD can produce a precise model of the vascular architecture and detect these signs. Central vascular flow, septal flow, irregular, and chaotic vascular architecture are associated with malignancy (62). Kalamantis et al. evaluated 318 women with unilateral adnexal mass using 3D PD. They reported a sensitivity, specificity, positive predictive value, and negative predictive value of 93.5, 92.9, 84.5, and 97.2 %, respectively (63). Several other studies provided similar results and concluded that 3D PD is a highly sensitive and specific tool for diagnosing ovarian malignancies (64-66). 3D USG and 3D PD technique were found to be highly reproducible (67-68).

Using quantitative evaluation of the global vascularity by vascularity index (VI), flow index (FI) and vascularity flow index may give a more objective idea about the total vascularity. Though lot of standardization is still required as far as the 3D power Doppler indices VI (vascularity index), FI (flow index), VFI (vascularity flow index) are considered. This can be done by gathering vascularity information by using a standardized, always identical size, tissue volume sample from the most vascularized region and standardizing PRF (pulse repetition frequency) and gains (69).

It is also important to note that even when no lesions are seen in the ovary, in a post-menopausal women, evaluation of the ovary with doppler and 3D power doppler helps to pick up truly stage 1 tumours. While routine health checkups for post-menopausal women (57-65 years) in last 5 years, we screened about 75 females. As is known these patients usually have small solid looking ovaries, with no follicles and sometimes even difficult to locate when these are truly atrophic. Whenever the ovary is visible we use doppler for evaluate the flows and if the flow is seen, we usually evaluate these vessels for resistance index and also for 3D power doppler. Out of these 105 patients, in 4 patients we found significant vascularity in the ovaries on 3D power doppler and suspected malignancy and we proved to be correct on histopathological assessment after the surgery. It is important to note here that in these cases the ovarian vascular RI was  $> 0.5$ , but it was 3D power doppler that indicated a possibility of malignancy.

In the same study two patients had evidently benign looking cysts on B mode transvaginal scan, 3D ultrasound on tomographic ultrasound imaging and rendering revealed its suspiciously malignant nature and 3D power doppler shows abundant vascularity in its apparently thickened part of the wall which actually was a solid component. These were also proved to be serous cystadenocarcinoma on histopathological studies.

3D power Doppler data on tumor vessels architecture enabled us to make more accurately preoperative sonographic diagnosis of an early stage ovarian cancer. On the other hand, CA 125 serum level of 16,3 U/ml was in normal ranges, giving us a false negative impression of a benign ovarian tumor.

Standard oncological surgical procedure was performed, and histopathology reported stage IA endometrioid adenocarcinoma of the ovary.

What is important to stress from the previously described case for ovarian cancer screening studies to come?

3D power Doppler qualitative analysis of tumor angiogenesis allows accurate detection of the earliest appearance of ovarian malignancy, i.e. stage IA ovarian cancer;

At the present time, higher equipment costs and more sophisticated operator skills make 3D ultrasound technology ideally available in clinical and university hospital settings as a secondary screening tool;

As published by Holbert (70), and noted in the case above, routine screening for ovarian cancer by standard 2D ultrasound modalities, in terms of primary screening, is a valuable addition to the yearly examination in outpatient clinics and private gynecology office settings.

## 8. FUTURE ACTIVITIES AND MEASURES

Application of a new 3D ultrasound technologies on patients with «positive» standard ultrasound tests represents an innovation as compared with previous ovarian cancer screening trials. On this way, we plan to demonstrate for the first time that a secondary screening based

on morphologic and vascular parameters assessed by 3D ultrasound and 3D power Doppler imaging may improve early detection of ovarian cancer and accuracy of ultrasound screening strategy in high risk populations. Regarding this hypothesis, the primary end point of our screening trial will be to improve the highest positive predictive value of 20%, reached by multimodal screening, resulting in less than five operations for each ovarian cancer found as an excellent surgery to malignancy ratio.

## 9. CONCLUSION

Although a critical evaluation of the recently published screening trials has led to the conclusion that routine screening for ovarian cancer is not recommended at present, many efforts continue to identify new screening modalities in high-risk populations. It seems that potential balance of benefits, harms and costs of screening may be more favourable in women with an inherited predisposition for developing of ovarian cancer. In such groups, compared with general population, fewer women need to be screened for each case detected, prevalence of the disease is markedly higher and the ratio of false positives to true positives is lower.

But, because the bulk of ovarian cancers occur in the general population, there has been growing interest in the possibility of screening for those in a great risk, i.e. asymptomatic postmenopausal women. Two main strategies; multimodal and ultrasound based have emerged, both still with some limitations for implementation in a routine screening practice. For the first one, the great challenge now is to improve the sensitivity of serum CA 125 as a primary screening tool. The risk of ovarian cancer algorithm (ROCA), an exponential model using data from several prior scans and testing for an exponential rise in the value of the marker, is likely to improve greatly sensitivity of CA 125 as a first line screening test. On the other hand, ultrasound has favourable sensitivity in a primary screening, but positive predictive value (PPV) of an ultrasound based strategy is yet too low.

Recently published studies indicates that 3D power Doppler imaging can improve the ability to differentiate benign from malignant ovarian masses, increasing significantly specificity and PPV in ovarian cancer detection. Therefore, the problem of low PPV in ultrasound-only strategies may be solved by introducing of new 3D ultrasound technologies, used together in a secondary screening procedure. The possible role of 3D ultrasound and 3D power Doppler imaging in early and accurate detection of ovarian cancer is currently under evaluation through Zagreb Ovarian Cancer Screening Trial.

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# Epidemiology and Diagnostics of Prostate Cancer During COVID-19 Pandemic

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**Background:** Prostate cancer (PCa) is the second most common cancer in the male population and represents a major health problem, especially in developed countries, where older men are more prevalent in the general population. Analyzing recent data for European countries, the incidence is highest in Northern and Western Europe (>200 per 100,000), while the rate is lower in Eastern and Southern Europe, but shows a continuous increase. Globally, about 450,000 Europeans are diagnosed with prostate cancer each year, and prostate cancer was the second most common cause of cancer-related deaths in 2018, when it was the cause of death for 107,000 men in Europe. Global data for BiH indicate that PCa is the second most common cancer in the male population, or the third leading cause of death in men due to cancer. **Objective:** The aim of this study was to analyze (PCa) how PCa screening is the most controversial topic regarding statements described in the urological literature searching most important biomedical on-line databases. **Methods:** Authors used descriptive method for this systematic study based on the published literature, summarized through meta-analysis, to show that screening was associated with an increase in PCa diagnosis. **Results and Discussion:** Most of authors written about this topic and concluded that the greater detection of localized and less advanced PCa disease, but without benefits in the field of PCa “specific survival” and “overall survival”, “overdiagnosis” and “overtreatment”, leading to recommendations against systematic population screening in all countries, including Europe. The main diagnostic tools for diagnosing PCa are digitorectal examination (DRE), serum specific antigen concentration (PSA), transrectal ultrasonography (TRUS) and mp MRI, and the definitive diagnosis is based on pathohistological verification of cancer in prostate biopsy specimens or operative specimen. The indication for biopsy should be determined based on PSA levels and/or suspected DRE, depending on age, potential comorbidities and therapeutic consequences, and the indication for repeated biopsy is an increase or persistently elevated PSA, suspected DRE, “atypical small acinar proliferation” (ASAP), extensive high grade “prostatic intraepithelial neoplasia” (PIN) and positive multiparametric MRI of the prostate (PI-RADS ≥3). **Conclusion:** PCa volume assessment is based on DRE and PSA with the addition of multiparametric MRI, bone scan and CT, although there are new imaging modalities, such as PET/CT scan and Diffusion-weighted whole-body MRI. However, the cost-effectiveness” of these new approaches needs to be further assessed. Given that COVID-19 has imposed other priorities on all health systems, we hope that the diagnosis of clinically significant prostate cancer and adequate treatment is not questionable at this time.

**Keywords:** prostate cancer, DRE, PSA, TRUS, prostate biopsy, CT, MRI, skeletal scintigraphy.

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## **1. INTRODUCTION**

Nothing. Early detection of prostate cancer (PCa) using prostate-specific antigen (PSA) and prostate biopsy have been shown to reduce PCa mortality (1–3). However, PSA testing and the use of systemic transrectal ultrasound-guided biopsies (TRUSGB) have low specificity, resulting in unnecessary biopsies, pre-diagnosis of PCa, and potentially over-treatment (1). In contrast, systematic biopsy can also lead to a false negative biopsy result or misclassification of the tumor, so that a clinically significant tumor may remain undetected (4, 5). Magnetic resonance imaging (MRI) followed by targeted biopsies reduces unnecessary biopsies and over-diagnosis of clinically insignificant (indolent) PCa, and thus reduces over-treatment of PCa (4, 6–8). On the other hand, active patient monitoring also reduces PCa over-treatment. International clinical guidelines provide precise guidelines for the diagnostic evaluation of patients, and PSA screening has been synonymous with PCa overdiagnosis and therapy for many years. The fact that the decline in mortality caused by PCa is stagnant, and that it is on the rise again in some countries, has led to a loud thinking that it is time to change the recommendations made by the European Commission for PCa screening (9).

## **2. EPIDEMIOLOGY**

According to the latest data, Prostate Cancer is on the rise, and is the most frequent cancer in Europe with important consequences for healthcare systems. Every year, around 450,000 European men are diagnosed with Prostate Cancer. It has overtaken colorectal cancer, and is now the second commonest cause of male cancer death. Prostate Cancer killed 107,000 men in Europe in 2018 and thus, is not an indolent disease, killing more men than breast cancer kills women. It is a chronic disease that causes many emotional and social problems for patients and their families. Prostate Cancer is on the rise, and is the most frequent cancer in Europe with important consequences for healthcare systems. Every year, around 450,000 European men are diagnosed with Prostate Cancer. It has overtaken colorectal cancer, and is now the second commonest cause of male cancer death. Prostate Cancer killed 107,000 men in Europe in 2018 and thus, is not an indolent disease, killing more men than breast cancer kill women. It is a chronic disease that causes many emotional and social problems for patients and their families (9). EAU adopted as official document: “White paper on prostate cancer. Recommendations for the EU Cancer Plan to tackle Prostate Cancer” (16).

And according to data related to 2012, prostate cancer was the most common cancer of age-adjusted men, aged 65–74 years, with a mean age of 66 years (10). On the other hand, looking at the entire male population, PCa was the second cancer diagnosed in men, with an estimate that it was diagnosed in 1.1 million men worldwide in 2012, and accounted for 15% of all cancers diagnosed (11). Autopsy studies show that the prevalence of PCa up to 4 decades of age is about 5% (CI: 3–8%), and from 80 years of age 59%

(48–71%) (12). In general, the incidence of PCa in the world varies by geographical region, and is highest in Australia and New Zealand, North America, and Western and Northern Europe, mostly due to more aggressive use of the PSA test, as well as the older age of the male population. In those spaces. The incidence is low in East and South-Central Asia, while in Eastern and Southern Europe, where it was also lower, it began to show a continuous increase (11, 13). According to EUCAN data from 2012, Norway (193/100,000) and France (187.5/100,000) have the highest age-standardized incidence rates, followed by Moldova (30.5/100,000) and Albania (24.8/100,000) (14).

According to GLOBOCAN data from 2012, PCa is the second most common cancer of the male population in Bosnia and Herzegovina, and the third leading cause of death from cancer in the entire male population (12). According to the data for public health of Republika Srpska, the total number of new cases of PCa in Republika Srpska in 2011 was 247 men, and the incidence was significantly higher in men older than 65 compared to men younger than 45–65 years, and was 88.13/100,000 men in the age-adjusted group, which is less than the European average of 96/100,000. According to the same data Globocan 2012, in BiH the incidence in the age-standardized male population for PCa was 44/100,000, with a rate of mortality 15/100,000, while in the EU the incidence was 96/100,000, and the mortality rate was 19/100,000. According to the same data, lower rates than BiH were only in Ukraine, Moldova and Albania. Of the total number of newly diagnosed PCa patients at the UCCRS in Banja Luka, at the time of diagnosis, 59% had advanced or metastatic disease.

In terms of survival, there is still a difference in survival between men in Eastern Europe and others in the rest of Europe. According to EUCAN data from 2012, the European average mortality rate is 19.3/100,000 (14). Over the previous decade, the 5-year relative survival rate for PCa was on the rise, from 73.4% between 1999 and 2001 up to 83.4% in the period 2005–2007 (15). The latest data globally indicate that mortality is stagnant, but in some countries, mortality is rising again, as is the case in the UK.

With the expected increase in the duration of life, and the incidence of PCa, it is expected that the economic burden of the disease in Europe will increase significantly. The total economic cost in 2018 for PCa in Europe was about 9 billion euros, with a higher proportion of PCa during care in the first year after diagnosis, which was about 5.8 billion (16).

## **3. PROSTATE CANCER PRECURSORS**

Prostatic intraepithelial neoplasia (PIN) and atypical small acinus proliferation (ASAP) are considered precursors of prostate cancer (10). PIN consists of benign prostatic acinuses or ducts with cytologically atypical cells and is classified into Low-Grade PIN and High-Grade PIN (HGPN) (17). Evidence that HGPN is a precursor to some prostate cancers is the size and number of HGPN foci in adenocarcinoma patients compared to those without cancer, and as HGPN levels increase, more multifocal cancers occur.

Further, biomarkers and molecular changes in HGPIN show similarity to cancer (17).

However, a presence of PIN is not necessary for cancer to develop. LGPINs, especially those present in the transition zone, are not closely related to HGPIN (17).

ASAP presents a higher risk histology than PIN for prostate cancer (10). The probability of prostate cancer after recognizing ASAP is 40-50% (17).

#### **4. PROSTATE ADENOCARCINOMA**

The most common prostate cancer is adenocarcinoma and it represents more than 95% of prostate cancers. 60-70% of prostate adenocarcinomas originate from the peripheral zone, 10-20% from the transitional zone and 5-10% from the central zone. In cases when it occurs in the peripheral zone, most typically occur on the back of the prostate, where it can often be palpated by digitorectal examination.

For the prognosis of prostate cancer, it is important to determine the degree of differentiation of the tumor itself and the degree of disease progression. The Gleason system is the most commonly used grading system for PCa (10). The degree of differentiation of the tumor (degree) depends on the ratio of the size of the nucleus to the cytoplasm, hyperchromasia of the nucleus, the number of mitoses and changes in the structure of prostate tissue. PCa has a heterogeneous degree of cell differentiation within tumor tissue. For that reason, the definitive degree of PCa differentiation, the so-called The Gleason score is determined by transrectal biopsy of the prostate under ultrasound control, transurethral electroresection or after radical surgery. The most prominent pathological changes are observed in cancer samples, and they are given numbers; primary degree for change represented in more than 50% of the sample and secondary degree for change represented in less than 50% and at least 5% of the sample (10, 17, 18). 1 denotes well-differentiated carcinoma, and 5 denotes poorly differentiated or anaplastic carcinoma. The values are then added together, and the final Gleason score can have a value of 2-10. The Gleason score between 5 and 10 has the most diagnosed PCa, and the prognosis of cancer depends on it. Cancers with values of 2-4 are rarely diagnosed and are considered weakly aggressive, 5-6 mildly aggressive, 7 suggests that the cancer is moderately aggressive, and Gleason score 8-10 indicates highly aggressive cancer (19). A total Gleason score of 6 (3+3) is considered a relatively indolent disease. In the differentiation of moderate from high-grade tumor, the primary Gleason pattern is the most important determinant of biological risk. Thus, within the Gleason score of 7, tumors labeled 4 + 3 are much more aggressive than 3 + 4 (10, 17).

In 2014, the International Society of Urological Pathology ranked PCa grades from 1 to 5 in such a way that GS 2-6 represents ISUP grade 1, GS 7 (3+4) ISUP grade 2, GS 7 (4+3) ISUP grade 3, GS 8 (4+4 or 3+5 or 5+3) as ISUP grade 4 and GS 9-10 as ISUP grade 5.

Age at the time of diagnosis is also recognized as a

prognostic indicator. High-grade or locally advanced PCa in younger men are often more aggressive than when present in older men. The hereditary form of prostate adenocarcinoma usually manifests itself 6-7 years earlier than the sporadic form of the disease (20). The clinician's task is not only to diagnose PCa, but also to distinguish between aggressive and indolent disease. Therefore, screening programs should use the most significant risk factors to more accurately identify men who are more likely to have an occult disease and thus allow physicians to thoughtfully test those patients who would benefit most from detecting the disease (21).

#### **5. DIAGNOSTIC EVALUATION**

##### **5.1. Symptoms**

The symptoms caused by PCa are not specific, i.e., the same symptoms are present in benign prostate enlargement and chronic prostatitis. In the early stages of the disease, most patients do not have symptoms of the lower urinary tract, and when they appear, they are present as symptoms of filling (more frequent urges to urinate, urgent urges to urinate, nocturnal urges to urinate) or symptoms of urination. weak and intermittent jet, terminal dripping, feeling of incomplete bladder emptying). Locally advanced adenocarcinoma due to infiltration of the bladder trigonum can cause ureteral obstruction and consequent hydronephrosis with an increase in nitrogenous substances, and invasion of seminal vesicles can cause hematospermia or decreased ejaculate volume (10, 17). The metastatic stage of the disease may be clinically manifested by bone pain and/or pathological fractures due to expansive osteoblastic lesions, secondary anemia, edema of the lower extremities due to lymphatic obstruction, paraneoplastic syndrome associated with visceral metastases (brain, liver, coccygeal dysplasia), as a result of sepsis caused by uroobstruction, and even paralysis as a consequence of metastases in the spinal column and compression of the spinal cord. For these reasons, early detection is considered necessary, with the aim of identifying adenocarcinoma limited to the prostate (10, 17, 22).

The main diagnostic tools for diagnosis are DRE, serum PSA concentration and transrectal ultrasonography (TRUS) and TRUS biopsy, and the definitive diagnosis is based on pathohistological verification of adenocarcinoma in prostate biopsy specimens or surgical specimen (10, 17, 22).

##### **5.2. Digitorectal examination**

Digitorectal examination (DRE) is the first test in the diagnosis and assessment of local prevalence of prostate cancer due to its simplicity and possibility of wide application. Most prostate cancers, since they are localized in the peripheral zone of the prostate, can be detected by DRE, when the volume is about 2 ml or more. Cancers located in the central and transitional zones of the prostate cannot be diagnosed by DRE, which is a disadvantage of this examination. In about 18% of all patients, PCa is detected only by suspected DRE, independent of PSA levels. Suspect DRE in patients with PSA greater than 2 ng/mL

has a positive predictive value of 5-30%. Suspected (abnormal) DRE is a strong indicator for prostate biopsy as well as for higher PCa aggressiveness and should be an indication for prostate biopsy (23).

### **5.3 PSA testing**

The PSA measurement represented a revolutionary advance in setting up a PCa diagnosis. It was discovered in 1979, and its clinical application emerged in the late 1980s and 1990s when it evolved as an invaluable tool for determining the need for prostate biopsy, and then, after PCa diagnosis, for risk stratification and for monitoring the clinical response, for the selected treatment modality (2, 3). PSA is kallikrein, which is produced by prostate epithelial cells, and is organ-specific, not cancer-specific. Under normal circumstances, only small amounts of PSA circulate in serum in free and bound form (10, 18). Serum levels may be increased due to benign prostate enlargement (BPE), prostatitis, and other nonmalignant conditions, but it is closely associated with localized and advanced PCa (18). PSA, as an independent variable, is a better predictor of cancer than the suspected signs of DRE or TRUS.

Serum PSA levels of up to 4 ng/mL are generally used as cut-off values for "normal" and "abnormal" (18). PSA is not an ideal tumor marker. 20-40% of patients with prostate-restricted adenocarcinoma have a PSA value of less than 4.0 ng/mL, while a positive predictive value (PPV) of serum PSA at 4-10 ng/mL is only 20-30% (2, 3). At a serum PSA value greater than 10 ng/mL, PPV increases to 72% (10). In light of all this, reference ranges of PSA depending on age/ethnicity have been proposed (10). However, the results of the PCPT study, which included prostate biopsy regardless of PSA value, showed that there is no PSA level below which the risk of PCa drops to zero (24). The value of PSA therefore indicates the continuity of risk, i.e., the higher the PSA, the higher the risk of PCa (25).

There are several modifications of serum PSA levels that may improve PSA specificity in early PCa detection. These modifications include PSA density, PSA density of the transition zone, age-specific reference range, and PSA molecular forms. However, these derivatives and PSA isoforms, such as (cPSA-i.e., complex PSA), proPSA (precursor isoforms of PSA), BPSA (benign PSA), iPSA (intact PSA) have limited benefit in routine clinical practice and are therefore not included in European Association guidelines (26). Index F/tPSA is a concept widely used in clinical practice to improve the distinction of benign prostate enlargement (BPE) from PCa. This ratio is used to stratify PCa risk for men who have a PSA level of 4-10 ng/mL and a negative DRE. In a prospective multicenter study, PCa was found on biopsy in 56% of men with f/tPSA <10 ng/mL, and only in 8% of men with f/tPSA >0.25. (25). Nevertheless, this test must be taken with caution, as several pre-analytical and clinical factors may influence f/tPSA, such as fPSA instability, very large prostate volume, and test variables. For example, fPSA is unstable at a temperature of 4 degrees Celsius, but also at room temperature. In addition, the characteristics of the test itself can vary, and concomitant BPE in large prostate can

result in a dilution effect. Otherwise, f/tPSA should not be used clinically at tPSA >10 ng/mL or during monitoring with known and detected PCa.

There are two methods of measuring PSA over time: PSA velocity (PSAV) and PSA doubling time (PSADT). PSAV is defined as the absolute annual increase in serum PSA, and PSADT measures the exponential increase in serum PSA over time, reflecting relative changes. These two concepts may be prognostic agents in patients treated for PCa, but have limited value and use in the diagnosis of PCa. Prospective studies have shown that these measurements do not provide additional information compared to PSA itself (26). Prostate Cancer Gene 3 (PCA3) is a new marker, detected in urine sediment after prostate massage by DRE (27, 28). The price of the "Progens" PCA3 urine test is now commercially available. The PCA3 test is superior to total PSA and the percentage of free PSA in the detection of PCa in men with elevated PSA. The PCA3 test can be used with PSA as well as with other clonic risk factors in the nomogram as a diagnostic tool to decide on a first or repeat biopsy. The PCA3 score increases with "prostate cancer volume". The presence of elevated PCA3 in urine has PPV for the presence of cancer on prostate biopsy with an accuracy of 74.6% and is particularly useful in the assessment of men with previous negative prostate biopsy and an increase in PSA (10). The main indication for the use of the PCA3 urine test could therefore be in determining when prostate rebiopsy is required after the initial negative biopsy, but in this regard, the "cost-effectiveness" aspect should be considered.

### **5.4. Prostate biopsy**

The indication for biopsy should be determined based on PSA levels and/or suspected DRE. The patient's age (life expectancy), potential comorbidities, and therapeutic consequences should also be considered (29, 30).

The first elevated PSA level should not promptly indicate a hasty biopsy. PSA levels should be repeated after several weeks with the same test under standard conditions (no ejaculation, no manipulations such as catheterization, cystoscopy, or TUR, and no urinary tract infection) in the same diagnostic laboratory, using the same PSA test method. The standard for performing prostate biopsy is ultrasound-guided biopsy, and although the transrectal approach is used for most biopsies, some urologists prefer to use the perineal approach. The detection rate of PCa in perineal biopsies is comparable to the transrectal approach (31, 32). An ultrasound-guided perineal approach is a useful alternative in special situations, i.e., after rectal amputation. Prostate biopsy is performed through the peripheral zone of the prostate with possible additional samples of any abnormal zone detected by DRE/TRUS (29, 30). Traditionally, 6 samples were taken along the parasagittal line between the lateral edges and the middle of the prostate in the area of the prostate apex, middle part of the prostate and prostate base bilaterally (29, 30). However, several studies have shown that taking more than 10 samples from more lateral direct peripheral biopsies increases the PCa detection rate by 14-20% com-



pared to sextant biopsy, and now the position of most urological associations is to take sextant biopsies from each lobe of the prostate, i.e., a total of 12 biopsy specimens, which has become the most widely accepted method in recent times (29, 30). Although a small number of PCa originate from the transitional zone, biopsy and transitional zone slightly increased the overall detection of PCa, when a more extensive prostate biopsy is undertaken (29, 30). The Vienna nomogram suggests a sampling minimum of 8–18 depending on the patient’s age, prostate volume, and PSA value of 2–10 ng/mL to ensure 90% PCa detection safety. However, most initial biopsy studies show that a further increase in biopsy samples taken >12-14 or a saturation pattern does not bring significant benefit and does not contribute to the percentage of positive biopsies. From the aspect of saturation prostate biopsy, some studies have reported that the incidence of PCa detected with saturation repeat biopsy (more than 20 samples) is between 30% to 43% and depends on the number of samples taken during previous biopsies (33). In special situations, a saturating biopsy may be done with a transperineal approach. This can be detected by an additional 38% of PCa, but the incidence of urinary retention is high (10%) and this deficiency reduces its clinical application (34).

Prostatic samples taken from different locations are sent to the laboratory in separate vials and should be processed in separate cassettes. Before processing, the number of samples from the vials and the length of each sample should be recorded. There is a significant correlation between prostate tissue sample and PCa detection rate. To optimize the detection of malignant lesions, samples should be cut at three levels.

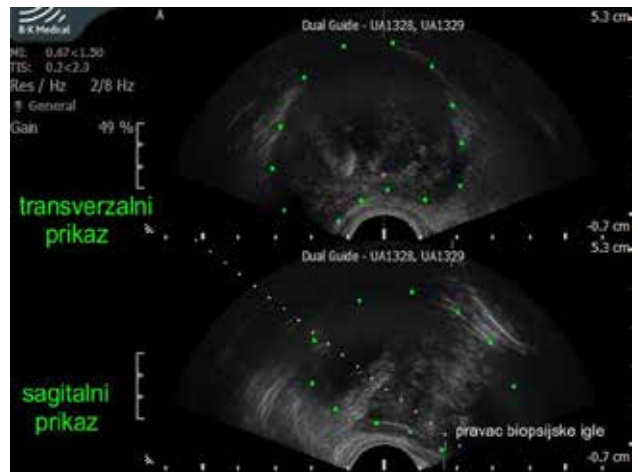
**5.5. Repeated biopsy**

Indications for repeated prostate biopsy are an increase or persistently elevated PSA, suspected DRE, ASAP, extensive PIN (multiple biopsy specimens and sites), and a positive multiparametric MRI finding.

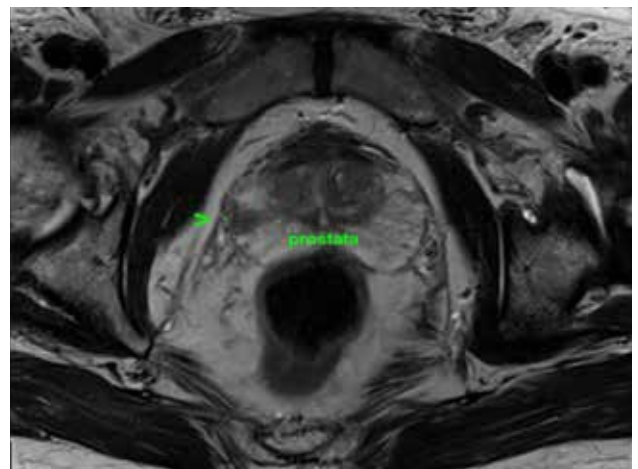
High grade PIN, as an isolated finding is not considered as an indication for repeated biopsy. Extensive PIN, or PIN in multiple biopsy sites, may be a reason for early repeat biopsy, because the risk of PCa increases. If clinical suspicion of PCa persists despite negative biopsies, MRI may be useful in examining the possibility of anterior localization of PCa, followed by TRUS or MRI-guided biopsy of the suspected area, and a positive multiparametric MRI finding (35).

**5.6 “Imaging” (transrectal ultrasonography / multiparametric MRI of the prostate)**

Transrectal ultrasound (TRUS) is the standard for diagnostic evaluation, and transrectal ultrasound-guided prostate biopsy (TRUSGB) is the standard for prostate biopsy (Figure 1). However, TRUSGB has its limitations. First, clinically insignificant (indolent) PCa are unnecessarily detected. Second, many men undergo TRUSGB and do not have a PCa. TRUSGB have complications, such as infections and bleeding, which also leads to increased treatment costs (36). Third, clinically significant PCa may remain undetected. Fourth, the observed risk stratification



**Figure 1. Transrectal ultrasound-guided prostate biopsy**



**Figure 2. Multiparametric MRI prostate with marked zone of suspected cancer**

errors lead to errors in the selection of the therapeutic modality for patients undergoing active surveillance for presumed low-risk PCa.

Multiparametric MRI (mpMRI) relative to TRUSGB, reduces the detection of insignificant PCa, while increasing the detection of clinically significant PCa (37-39). Selective localization of clinically significant PCa allows MR-directed biopsy and therefore fewer biopsy specimens are required (Figure 2). This improved the diagnostic evaluation for men with suspected PCa. If mpMRI is unsuccessful, hasty TRUSGB can be avoided (40, 41). Numerous multicenter randomized studies have confirmed the superiority of mpMRI and MR-direct biopsies over TRUSGB (42-47). Given the limitations present in these studies, a prospective multicenter study compared mpMRI + MRGB directly versus



**Figure 3. Bone scan with multiple metastases of prostate cancer**

TRUSGB in men with suspected PCa and concluded that MRI versus TRUSGB resulted in identical detection of clinically significant PCa, with no significant clinical significance. insignificant (indolent) PCa. In that high-quality study, almost half of the men did not have MRI suspicious signs on PCa, which is more than in other studies. Failure to perform TRUSGB resulted in the loss of only 4% of clinically significant PCa, so patients may benefit from MRI, because biopsy can be avoided in half of men with indolent PCa detection without compromising the detection of clinically significant PSA, as well as the required smaller number biopsy specimens for diagnosis (48). In any case, we must remember that in diagnosing PCa, after DRE and PSA have been performed, no imaging modality (TRUS/mpMRI) can shift the prostate biopsy and the pathohistological diagnosis it provides. The requirement for optimal assessment ranged from “sextant” to extended biopsy and from extended to saturation biopsy, with the goal of reducing random sample bias and improving disease staging. The next step certainly represents the use of a targeted biopsy into the suspect zone seen in multiparametric magnetic resonance imaging. The technique of these targeted biopsies predominantly detects “higher grade PCa” while losing “low-grade areas”.

### **5.7. Clinical “staging”**

In clinical staging, PCa volume assessment was based on DRE and PSA with the addition of mpMRI, skeletal scintigraphy (bone scan) and CT. The TNM classification is used to determine the extent of the disease. The TNM system is an abbreviation where T is used to evaluate the extent of the primary tumor, N is used to express the involvement of lymph nodes, while M indicates the existence of the spread of the disease to distant parts of the body. Assessing the prevalence of PCa by TNM system before treatment is called “clinical” TNM classification of prostate cancer, as opposed to possible postoperative assessment of the stage of the disease by microscopic analysis of tissue and is called “pathohistological” (p) TNM classification of prostate cancer. The pTNM classification differs from the TNM classification for clinical stages T1c and T2 substages. All pathohistologically confirmed PCa after radical prostatectomy, which are “organ-confined”, are classified as pathological stage T2, and currently the Union for International Cancer Control (UICC) no longer lists pT2 substadiums. Transrectal ultrasound (TRUS) and mpMRI are indicated in T-staging. In the assessment of nodal status (N), the use of CT and MRI, Choline PET/CT and/or prostate-specific membrane antigen-based PET/CT (PSMA PET/CT) is indicated. In the assessment of M status, the use of skeletal scintigraphy (bone scan), Fluoride PET and PET/CT, Choline PET/CT and MRI of the whole body is indicated (Figure 3).

## **6. PSA “SCREENING” AND EARLY DETECTION OF PCa: YES OR NO?**

Detection of the disease in the presymptomatic stage is called secondary prevention and despite the apparent benefits of PCa screening, its application in clinical prac-

tice has been the subject of significant controversy, both in the USA and in Europe. Following PSA screening, which has become widespread since the 1990s, the U.S. has had a 2% increase in PCa incidence per year during 1995, and has been steadily increasing since then, approximately 1% per year, even as the mean age at setting diagnoses of PCa decreased to 66 in 2011 (49-52). Epidemiological data further show a 40% reduction in mortality and 75% fewer patients with locally advanced disease at the time of diagnosis. Currently, of the 1,000 age-adjusted men undergoing PSA screening, 240 will have a positive finding and 100 will have a positive prostate biopsy for PCa (53). However, 20–59% of these tumors carry a low risk of metastasis or shortening of an individual’s lifespan (44). Nevertheless, 80 out of 100 patients will choose surgical treatment or radiotherapy (53). And this is the basic argument against screening, which identifies many indolent PCa that will never result in clinically significant PCa, which is a phenomenon of excessive disease detection and over-treatment (53). These attitudes were basically grounded for the first time in 2009 after the publication of the long-awaited results of two prospective, randomized studies.

One of them, The Prostate Lung Colorectal and Ovarian (PLCO) Cancer screening included 76,693 men aged 55-74 in 10 centers in the United States for annual screening using PSA and DRE (working group) or standard care as a control group. After 7 years of follow-up, the incidence of PCa per 10,000 persons/year was 116 (2820 cancers) in the screening group and 95 (2,322 cancers) in the control group (54). The incidence of death per 10,000 individuals per year was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group. 44% had lower prostate cancer specific mortality in men without or with single comorbidity. The PLCO project team concluded that PCa-induced death was very small and insignificantly different between these two groups of subjects.

The second study, The European Randomized Study of Screening for Prostate Cancer (ERSPC) included 162,243 men from 7 European countries, aged 55-69 years. Men were randomly selected for the PSA screening group on average once every 4 years and for the non-screening group (control group). During the mean follow-up of 9 years, the cumulative incidence of PCa was 8.2% in the screening group and 4.8% in the control group. The “Rate ratio for death of PCa” was 0.80 (20% less) in the screening group compared to the control group. The “absolute risk difference” was 0.71 deaths per 1,000 men. This means that 1410 men had to undergo screening to detect 48 additional PCa cases, which needed to be treated to prevent one PCa death. The ERSPC concluded that PSA screening reduces PCa mortality by 20%, as well as 41% reduction in metastatic disease at the time of diagnosis with screening, but is associated with a high risk of “over-diagnosis” (55).

However, after 11 years of follow-up, the ERSPC found that prostate cancer death was 0.79 in favor of screening (56). A subanalysis of patients from one ERSPC study center with a follow-up period of 14 years confirmed a mortality reduction of almost 50%, which could neverthe-

less be a favoring factor for PCa screening (50, 57, 58).

A recent study, with a subanalysis of patients from the ERSCP study in Rotterdam pilot study 1 in a cohort of men randomized in 1991-1992. and for a follow-up period of 19 years provided data on a further reduction in metastatic disease in subjects who were in the screening program than previously reported. The overall relative risk of metastatic (M+) disease and prostate cancer (PCa) death was 0.46 (95% confidence interval (CI):0.19-1.11) and 0.48 (95% CI:0.17-1.36), in favor of screening. This ERPC Rotterdam pilot study 1, presented in a period without significant contamination, shows that PSA-based screening could result in a significant reduction in M+ morbidity and mortality, which, if confirmed in larger data sets, should encourage further discussion of advantages and disadvantages of PSA screening (59).

Recent data from The Surveillance, Epidemiology, and End Results (SEER), which provide data on cancer statistics with a view to reducing cancer in the US population, and which challenge PSA screening, suggest that between 2011 and 2013, the overall incidence of PCa declined each year in all age groups and races while the rate for age-adjusted men decreased from 147.7/100,000 men in 2010 to 108 in 2013 (56). The National Cancer Database revealed a small increase in the clinical phase of T3 tumors or higher from 2011 to 2013, as well as an increase in the incidence of metastases during the same period (56, 60, 61). Gaylis et al. presented data on the increase in the proportion of Gleason 8 cancers, from 21% in 2011 to 30% in 2014, as well as the increase in Gleason 8-10 cancers (61). Analysis of all Gleason Score 8-10 biopsy specimens increased from 15% in 2010 to 25% in 2015 (61, 62).

## 7. CONCLUSION

Since 1997, there has been a threefold increase in the incidence of prostate adenocarcinoma, and PSA screening has made a significant contribution to this. Although mortality caused by prostate cancer, especially in the last 1-2 decades, has had a declining trend, more than 92,000 men in Europe still die from PCa each year. Therefore, PCa in some European countries has become the second leading cause of death in the male population from cancer, after mortality caused by lung cancer, and ahead of mortality caused by colorectal cancer. The decades-old view that mass PSA screening is not indicated because of the risk of pre-diagnosis and over-treatment is slowly coming into question. On the other hand, the introduction of prostate MRI and MR guided prostate biopsy reduced the number of unnecessary biopsies and detection of indolent PCa. Subanalyses of the PLCO and ERSPC studies, which are performed after a long follow-up period, however, indicate that PSA screening leads to a reduction in the incidence of metastatic PCa and a reduction in PCa-induced mortality. The latest data, which show that mortality caused by prostate cancer is stagnant and that it is on the rise in some European countries, imposes the need to reconsider attitudes about PSA screening by leading international associations. In this regard, the views are fo-

cused on the expectation of changes in the guidelines in terms of the introduction of prostate cancer into routine screening by the European Commission.

Given that COVID-19 has imposed other priorities on all health systems, we hope that the diagnosis of clinically significant prostate cancer and adequate treatment is not questionable at this time (63). However, routine screening of the age-adjusted men, with an increased risk of prostate cancer, is certainly questionable.

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# The Laparoscopic Surgery: History, Technique, Ergonomic and Specifics in the Time of COVID-19

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**Background:** Laparoscopic surgery is a very modern and sophisticated method of surgical treatment and as such requires different equipment, different equipment layout, surgical team and a special patient position. The first human laparoscopy was performed by von Jacobeus in 1910 in Sweden, to diagnose ascites and this method was mainly used by gastroenterologists. Since 1980, after the first laparoscopic surgeries, such as laparoscopic appendectomy, cholecystectomy, laparoscopic colon surgery etc., surgeons have taken a leading role in the application of laparoscopy. **Objective:** A laparoscopic surgeon should work slowly and safely, stop work if he does not have a good examination of the operative field, and his technique is dominated by good control of hemostasis. Ergonomic specifics of instruments, equipment, and specific position of the surgeon during the operation are important in laparoscopy. The application of laparoscopic surgery in patients with COVID-19 infection is the topic of this article. **Methods:** We analyzed all patients operating laparoscopically who were simultaneously infected with COVID-19 virus. **Results/Diskussion:** Laparoscopic surgery has numerous advantages compared to open surgery, which has been established in clinical studies: faster recovery of patients, fewer complications, less pain, aesthetic results are better, and the economic effects are on the side of laparoscopy. The application of laparoscopic surgery at the time of COVID-19 infection requires some answers that we do not yet have. Is there a possibility of contamination of the surgical team with gas from the abdomen? Does increased intra-abdominal pressure adversely affect a COVID-19 infected patient? All of this requires the larger clinical trials that await us. **Conclusion:** Laparoscopic surgery has an advantage over open surgery in standard conditions. In patients infected with COVID-19, the use of laparoscopic surgery is associated with certain aggravating factors that require additional clinical trials.

**Key words:** Laparoscopic surgery, technique, ergonomics, COVID-19 infection.

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## 1. HISTORICAL BACKGROUND

Minimally invasive surgery and laparoscopy in particular represent the conventional approach to most abdominal and pelvic surgery. The popularity of these techniques is due to many documented advantages, such as short hospitalization, rapid recovery after surgery, higher precision of the surgical maneuvers, and less bleeding. Often, such minimally invasive operations are performed in essentially the same manner as are traditional surgical procedures but in other instances, an entirely new operative technique has been developed to accommodate this technology (1-3).

The indications for laparoscopy or minimally invasive surgery can be divided between the diagnostic and therapeutic indications. Diagnostic laparoscopy includes evaluation of acute or chronic liver disease, to determine eti-

ology of chronic abdominal pain, diagnosis of unstaging of intraabdominal malignancies or evaluate selected tumors for their response to chemotherapy. Also, there are a few emergency applications for determining the cause of acute abdominal pain or peritonitis and also in selected individuals, after blunt or penetrating abdominal trauma. Therapeutic laparoscopy includes: laparoscopic cholecystectomy, appendectomy, splenectomy, laparoscopic colon surgery, laparoscopic hernia repair and many other procedures. Some of these procedures have already been accepted as the method of choice, e.g. laparoscopic cholecystectomy, appendectomy, hernia repair and colon resection (2,3, 4,5,6).

The first experimental laparoscopy was done in Berlin in 1901, by the German surgeon Georg Kelling (1860-1945), who with the help of a cystoscope insufflated air into the

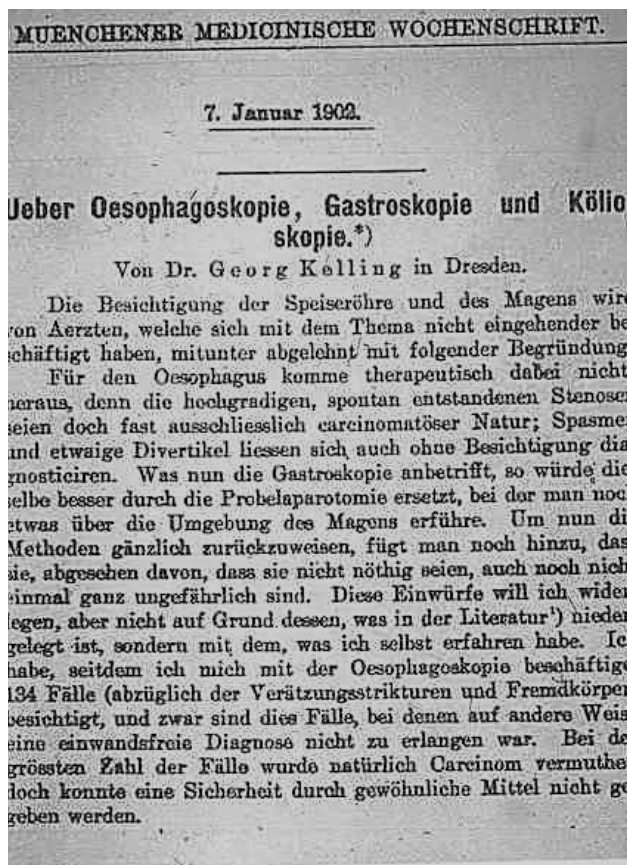


Figure 1. G. Kelling's research on laparoscopy

dog's abdomen and then examined it. Dr. Kelling first presented his observations on laparoscopy at the Congress of German Physicians in Hamburg in September 1901.7,8 He published articles on laparoscopy, which he initially called "celioscopy" (7,8).

The first human laparoscopy was performed by von Jacobaeus in 1910 in Sweden, to diagnose ascites(8,9). He was a great enthusiast, publishing his articles on endoscopic surgery in Germany, France and Sweden. In 1912, he published a monograph in which he described in detail laparoscopies performed from 1910-1912. in Stockholm (5,8,9).

Significant progress in laparoscopic surgery was noted in 1938 when a special spring-loaded needle was introduced to insufflate the abdomen. Janos Veres (1903-1979) introduced a new type of spring-loaded needle to drain abscesses and air from the thoracic cavity in patients with tuberculosis. The idea was reached that the needle could be suitable for insufflation of the abdomen with gas, and with certain small modifications, this needle was used in laparoscopy and as such is still present today. In 1960, Kurt Semm, a German gynecologist, introduced an automatic insufflator, then an electrocoagulator, and an irrigation and aspiration system. Semm, who worked at Kiel, enriched laparoscopic surgery with many surgical procedures. K.Semm was the first to perform a laparoscopic appendectomy in 1980, publishing his article in the journal „Endoscopy“ in 1983. (2,7,11). The introduction of a video camera mounted on a laparoscope in 1986 allowed surgeons to more casually monitor events in the abdominal cavity and act by monitoring everything on the screen.



Figure 2. The first human laparoscopy published

The first human laparoscopic cholecystectomy using a modified rectoscope with CO2 insufflation was performed by the German surgeon E. Muehe in 1985 at the district hospital in Boeblingen . Although his summary of the article was published in the Langebecks Archive of Surgery In 1986, it went unnoticed. It was not until 1994 that this information began to be mentioned and treated as the first laparoscopic cholecystectomy performed (11,12).

Philippe Mouret in Lyon performed the first laparoscopic cholecystectomy in France in 1987(13). The following are laparoscopic cholecystectomies in the United States performed in 1988 by B. Mc Kernan and W. Saye (5). The first Nissen funduplication was performed in 1987(15), the first laparoscopic colon resection was performed in 1991, by Jacobs et al., (16).

The first laparoscopic cholecystectomy at the Surgical Clinic of the University Clinical Center Tuzla was performed on September 12, 1997. under the mentorship of Professor Richard G. Azizkhan.

## 2. TECNIQUE OF LAPAROSCOPIC SURGERY

### 2.1. Patient position and equipment

Laparoscopic surgery is a very modern and sophisticated method of surgical treatment and as such requires different equipment, different equipment layout, surgical team and a special patient position. Preoperative preparation is standard as with the open method (nasogastric suction, urinary catheter, etc.). It is necessary to check the correctness of the equipment and make its schedule before the surgical intervention. Depending on the type of surgery, the surgeon, assistant and nurse stand on either side of the operating table. In upper abdominal surgery, the surgeon often assumes a position between the patient's abducted limbs, the so-called "European" position, in order to be able to manipulate instruments more easily. A modified Lloyd-Davies position (lithotomy position) is mandatory in cases of abdomino-perineal procedures, or in esophageal or gastric surgeries(17,18). Complete or partial lateral position of the patient is required for kidney





Figure 3. Patient positions in laparoscopic surgery

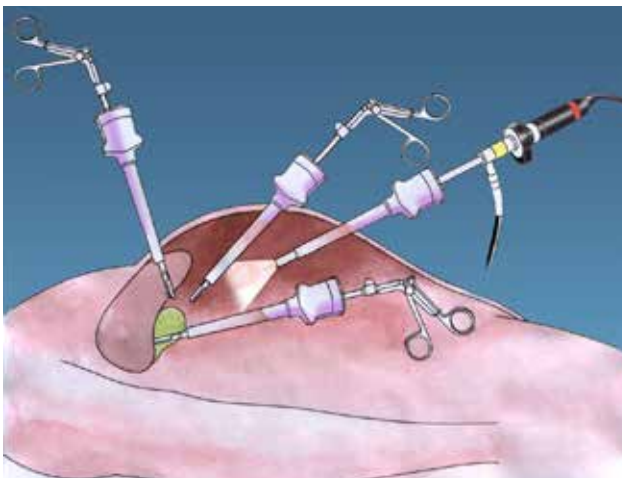


Figure 4. Schematic representation of laparoscopy

or adrenal surgery. The standard positions of the patient during laparoscopy are shown in Figure 3.

### 2.2. Establishment of pneumoperitoneum

Most of the difficulties during laparoscopy are due to the need to fill the abdominal cavity to a certain pressure with gas, which is further maintained during the operation via a needle or trocar inserted through the abdominal wall (Table 1; Figure 1).

Pneumoperitoneum with CO<sub>2</sub> has been used in clinical practice since the introduction of laparoscopic cholecystectomy in the late 1980s. Physiological changes that occur in the body during laparoscopy are the result of various influences. First of all, there are the effects of in-

### PNEUMOPERITONEUM ESTABLISHMENT TECHNIQUE

- Transumbilical insufflation
- Insufflation through the upper left quadrant
- Insufflation in place of the PALMER point
- Insufflation through the ninth intercostal space
- Transuterine insufflation

### OPEN TECHNIQUE

- Direct blind placement of the trocar
- Positioning the trocar by visual inspection

Table 1. Techniques of laparoscopic surgery

creased intra-abdominal pressure (IAP) on the body, the consequences of CO<sub>2</sub> resorption, and we should not ignore the surgical trauma, which is caused by the operation itself. Carbon dioxide is the most suitable gas for insufflation into the abdominal cavity, because it meets several important criteria: not flammable and it is possible to use electrocoagulation, very soluble in blood and tissues, it is easily eliminated through the lungs, is non-toxic and it is inexpensive (19,20,21).

Increased intra-abdominal pressure during laparoscopy (12-15 mm/Hg) has different effects on different abdominal organs acting through two mechanisms: directly and indirectly. The direct effect of pneumoperitoneum is a consequence of the mechanical action of the gas, and increased intraabdominal pressure (IAP). The indirect effect of PNP is caused by absorption of CO<sub>2</sub>. Increased intra-abdominal pressure (IAP) mechanical effect on all intraabdominal organs and tissues, bringing different pathophysiological responses, which were mostly transient. Increased intra-abdominal pressure supports splanchnic vasoconstriction and reduction of flow through the inferior cava vein, renal vein, and portal vein, all resulting in decreased venous flow to the heart. During laparoscopic procedures increased IAP leads to increased intracranial pressure (ICP), disrupts the flow of blood through the intracranial blood vessels and leads to abnormal resorption of cerebrospinal fluid (Table 2). Working with low pressure or gassless laparoscopy prolaune can drastically reduce the negative effects of increased intraabdominal pressure during laparoscopy (21-26).

### 2.3. Trocar arrangement

Proper placement of the trocar is an essential step in laparoscopic abdominal surgery. The constitution and anatomical structure of the patient, previous abdominal surgeries, and the surgeon's experience are additional factors that affect the number, size, and arrangement of secondary trocars (2). The secondary trocars should be as far away from the primary trocar as they are from each other. This avoids the possibility that one instrument may interfere with another during operation or that the working paths of the instruments intersect. If the trocars are too close to each other, there may be interposition of instruments and interference during work in the surgical field. In principle, the secondary trocars should be placed at an angle of 90° to the primary, forming an equilateral triangle around the operating field. Preoperative marking of the site of secondary trocars with a skin

ABDOMINAL HYPOPERFUSION CAUSED BY INCREASED INTRAABDOMINAL PRESSURE (IAP)

- Hepatoporal effects
  - transient hypoperfusion of hepatocytes
  - increase in aminotransferases
  - decreased flow through the portal vein and hepatic artery
- Flush effects
  - Reduced flow through the stomach and other organs
- Renal effects
  - reduction of renal blood flow
  - less glomerular filtration
- increased venous path in the lower extremities and abdomen

Table 2. Abdominal hypoperfusion caused by increased intraabdominal pressure (IAP)(26)

marker can help determine the exact site of insertion of secondary trocars(2,27,28)

The most favorable position of the secondary trocars is to be placed in front of and on the side of the primary trocar through which the laparoscope was introduced, because this makes hand-eye coordination easier, and the instruments are constantly in sight. Placing the instruments in one line makes it difficult to maneuver the instruments needed during the operation (2,27,28,29). Secondary trocars should be kept at a certain angle in relation to the horizontal position of the body. Most often, this angle is 45-125° (optimally at 65°) for easier ability to work and reduce the possibility of crossing instruments outside the abdomen or in the abdomen(2, 27). Proper placement of the trocar can: minimize instrument interference, optimize ergonomics, reduce mental and muscular

fatigue, reduce loss of time and effort, increase work safety, ensure good surgical practice.

**3. PRINCIPLES OF SPECIMEN REMOVAL**

Small incisions during laparoscopic procedures are a great advantage of this method, but it is difficult to remove large tissue preparations through small incisions. On the basis of the above, various techniques of removing tissue preparations from the abdominal cavity have been developed without increasing the number and size of incisions in the abdomen. There are several basic ways to extract tissue preparations from the abdomen: directly through the trocar cannula, directly through the trocar incision, through a new separate incision of the abdominal wall, or through natural body openings (transanally, transvaginally). Endoscopic disposable bags for removing tissue preparations from the abdomen have many advantages and there are special situations when their use is mandatory. The technique of application of endobags is simple and should be used in everyday work, especially in cases of preparations with malignant cells, large preparations that must first be fragmented, highly inflamed preparations, etc. (Figure 5).

**4. ERGONOMIC SPECIFICS OF LAPAROSCOPY**

The position of the surgeon during the laparoscopic technique of work, in relation to the traditional, open surgery, is completely different. Ergonomics has been completely changed compared to open surgery. The position of the surgeon and the visualization of the operative field

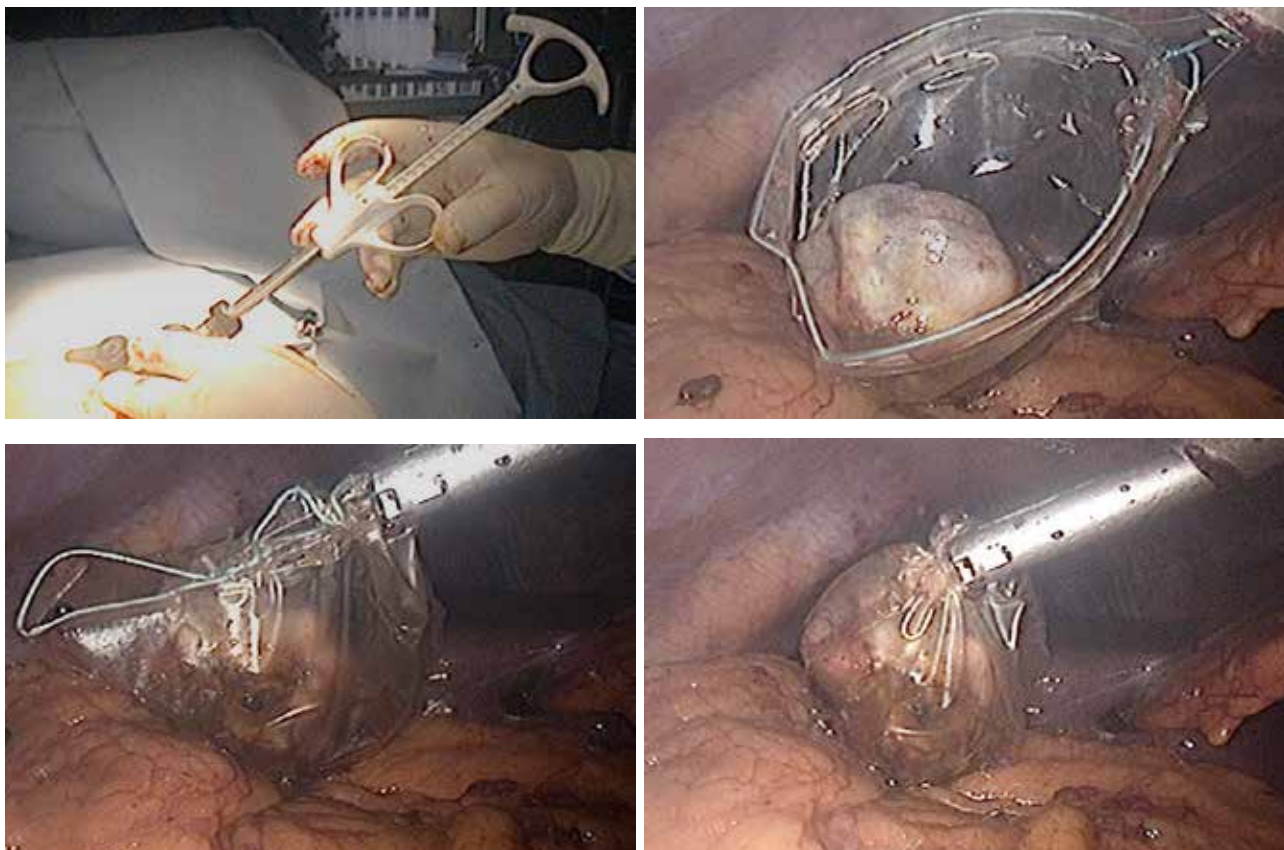


Figure 5. Removal of the gallbladder from the abdomen using an endo-bag





Figure 6. The position of the surgeon and eye-hand coordination in open and laparoscopic surgery

are completely different from that of traditional surgery (Figure 6) (31,32). The tactile sensation that surgeons used extensively during the traditional open method is no longer so important and has almost completely lost its significance in laparoscopic technique (33). The movements of the instruments used by the surgeon during laparoscopy are inverse, the instruments are longer and with limited movements (34). Good and complete coordination of movements in open surgery is natural, while in laparoscopic technique this coordination must be learned and practiced (35).

Problems with the position of the surgeon occur due to two things: due to the standing position of the surgeon and due to the length of the operation. Standing position of the surgeon and the whole team during laparoscopic surgery leads to stress and fatigue of the muscles of the whole body (36,37). During laparoscopic work 70% of the work is done standing still (38). Compared to standing during the open method of work, during laparoscopy the surgeon stands higher upright, with reduced body movement and less displacement of body weight than with open surgery(39). Special positions of the surgeon during certain laparoscopic procedures also lead to special problems for the surgeon. Laparoscopic surgeries in which the surgeon stands on the patient's side lead to fatigue and strain on the shoulder muscles (40).

Therefore, laparoscopic surgeons usually stand for a long time during the operation, more or less statically and upright, with less movement of the head and neck and with less movement of body weight than with open surgery. Physical, mental and visual strain on laparoscopic surgeons can lead to the "laparoscopic load syndrome" described in laparoscopic surgery. In more severe forms, this syndrome is manifested by mental exhaustion, increased nervousness and irritation of the surgeon with a reduction of all psychomotor abilities (39,40).

Good and complete coordination of movement in open surgery is natural, while in laparoscopic technique this

coordination must be learned and practiced.

## 5. EMERGING TRENDS

Even less invasive approaches have been developed in recent years, such as the use of very thin instruments in mini- and micro-laparoscopy and the development of single-port access laparoscopy (SPAL) (41,42). These evolutions that minimize the port size in the case of mini-laparoscopy or reduce their number by using only one entrance, as in SPAL or transvaginal natural orifice transluminal endoscopic surgery (vNOTES), could be even less invasive

## 6. LAPAROSCOPY IN THE COVID-19 ERA

The novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) that emerged in China at the end of 2019 has spread to a pandemic infection in just a few months. Laparoscopic surgery during the COVID-19 pandemic has its own specifics. We need to answer a few questions that are still unknown to us. First of all, is it possible to contaminate the surgical team and the operating room during laparoscopy. Can CO<sub>2</sub> released from the abdomen in infected patients lead to team infection? Also important is the question of whether increased intrabdominal pressure can worsen the condition of an infected patient who has undergone laparoscopic surgery. The ability to work with low insufflation pressure (6-8 mm / Hg) may be more favorable for infected patients. To date, there are no clinical studies that have addressed this problem.

Primum non nocere: First, do no harm. This is a professional and ethical imperative with which we as physicians are very familiar (42-44). Can we expand this principle to include the patient and the healthcare team? Certainly, in this period, the surgical indications and accurate patient selections should be thoroughly discussed in each case, since it is mandatory to reallocate medical and paramedical staff to face the emergency.

## 7. CONCLUSION

Laparoscopic surgery is a modern surgical technique and forms the basis of modern surgery. It has many advantages over open, conventional surgery. Under certain conditions, there are limits that need to be well known. The laparoscopic technique of work requires a good knowledge of the pathophysiology of the pneumoperitoneum in the complications it can cause.

Other complications of laparoscopic surgery are similar to those of open surgery. Uniport laparoscopy has advantages over multiport but not so much that it should be insisted on. Adequate patient selection is important in determining the type of laparoscopic technique we will apply. A good knowledge of standard laparoscopic surgery is required, which involves a standard intrabdominal pressure of 12-15 mm / Hg and the use of multiple ports. There are currently no clear guidelines as to whether coronavirus-infected patients (COVID-19) should be required to undergo laparoscopic surgery and whether there is a risk to the surgical team rather than an open procedure.

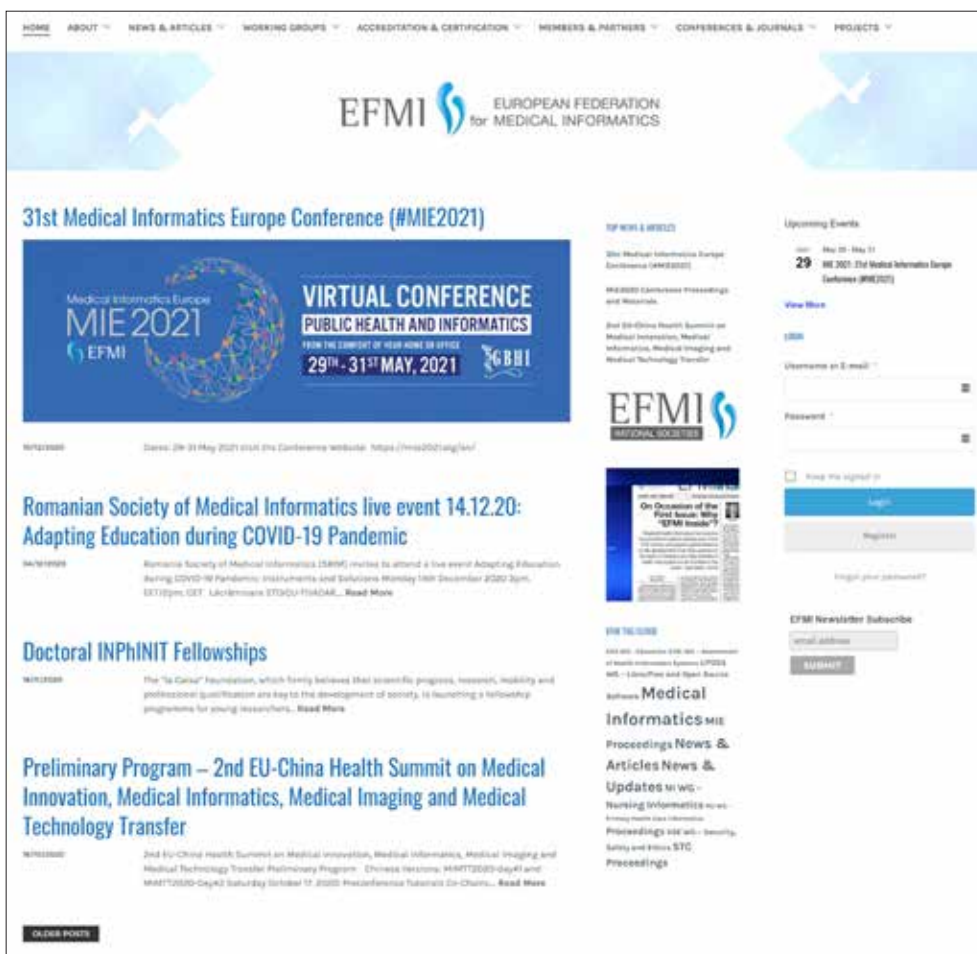
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# Predatory in Scientific Publishing—a Burning Issue in Science

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**Background:** Predatory publishers and so-called hijacked or fraudulent journals, are threats to the quality of published articles and waste valuable research and manuscripts when scholars and authors submit and publish their works in these journals. **Objective:** The aim of the paper is to point out the problem, causes and consequences of predatory publishing, characteristics and features of predatory publishers and fraudulent or fake journals and how to prevent and avoid publishing in such journals. **Methods:** Exploring the web blog of Jeffrey Beall and debate about Beall's list of predatory publishers and journals and review of the relevant published literature, as well as personal experience and observations of the author. **Results:** Jeffrey Beall, an American librarian and library scientist from Denver, University of Colorado, has drawn attention to "predatory open access publishing" and created widely known Beall's lists of potentially predatory publishers and open-access predatory journals publishing submitted manuscripts promptly without the reviewing process and with a high rate of publication fee. The debate initiated by Jeffrey Beall is continuing in the scientific community with increased number of authors and published articles on this still unresolved issue in the last about 10 years. The features of fraudulent or fake journals, threats and consequences are discussed as well. **Conclusion:** Increasing awareness in the scientific community is essential how to differentiate trustworthy-reliable journals and predatory ones and to avoid predatory journals. Continuous education of authors about predatory publishers and journals, both the existing and the newly-emerging wave of scholars, must be the purpose and the imperative of the academic community. In order to protect the peer review process, the academic and scientific community must set the criteria for scientific advancement by not recognizing and valuing the articles published in the predatory journals.

**Keywords:** predatory publishers, fraudulent journals, hijacked journals, open access.

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## 1. BACKGROUND

The Predatory publishers and journals, so-called hijacked and fraudulent-fake or "pseudo" journals, are threats to the quality of published articles and waste valuable research and manuscripts when scholars and authors submit and publish their works in these journals. Predatory publishers exploit the open access and author-pays model damaging scholarly publishing and promoting unethical behavior by scientists. The most of scholars are oriented to submit and publish their papers in legitimate journals. But, the huge proliferation of journals, both legitimate and predatory, makes it often difficult to recognize and avoid predatory journals. (1, 2)

Predatory publishing is the publisher's practice of unethically taking advantage and exploiting the gold open access model for publishing journals without meeting scholarly publishing standards in order to gain financial profit via article processing charges (APC) without proper review, undermining the review process which is hallmark of traditional scholarly publishing. (1-3).

## 2. OBJECTIVE

The aim of the paper is to point out the problem, causes and consequences of predatory publishing, characteristics and features of predatory publishers and fraudulent or fake journals and to increase awareness and warn scholars, especially young researchers, how to recognize and how to prevent and avoid submission of their manuscripts for publishing in such journals.

## 3. THE BEALL'S LIST OF PREDATORY PUBLISHERS AND JOURNALS DEBATE

Jeffrey Beall is an American librarian and library scientist from Denver, University of Colorado, who drew attention to "predatory open access publishing" more than 10 years ago and created two widely known Beall's lists: a) Beall's list of "Potential, possible or probable predatory scholarly open-access publishers"—applying unprofessional practices, from undisclosed charges and poorly defined editorial hierarchy to poor English, and b) Beall's list of predatory open-access journals -publishing sub-



mitted manuscripts promptly without proper review process and with a high rate of publication fee (1, 4, 5). Beall's lists were compiled on criteria based in part on two policy statements—the COPE Code of Conduct for Journal Publishers (6), transformed in 2017 into COPE Core Practices (7) and the Principles of Transparency and Best Practice in Scholarly Publishing from WAME, COPE, DOAJ, and Open Access Scholarly Publishers Association (8). Beall's website was dismantled for unclear reasons in Jan 2017 (9).

Jeffrey Beall made the first steps to investigate a journal's or publisher's authenticity and initiated a debate about the value of the Beall's lists and activities related to prevention and fighting with such publishing misconduct and “academic corruption and racketeering”. But, he didn't list the specific criteria he used to categorize a given journal as predatory and he mistakenly black-listed some legitimate journals and publishers, especially from low and middle income countries (1).

On the other side Beall was exposed to severe critics blaming him that he is not authorized and competent expert in the field as a librarian to evaluate scholarly academic journals, as well as that he is using double standards and discrediting the Open Access Journals, in general, as predatory or fraudulent journals, especially those from developing countries, without sufficient evidence for proper clear objective methodology to evaluate the quality of journals in different disciplines (5, 10,11).

The validity of Beall's lists was confirmed by Bohannon's study-experiment and paper published in *Science* in 2013. Within the period of 10 months Bohannon submitted 304 versions of the wonder drug paper, from the same fake cancer cell growth study, to different open-access journals, 167 from the DOAJ, 121 from Beall's list, and 16 that were listed by both. More than half of the journals, exactly 157 or 52%, accepted the paper failing to notice its fatal flaws, 98 (32%) rejected, and 49 or 16% of the journals were undecided. Only 36 of the 304 submissions generated review comments recognizing some of the paper's scientific problems and 16 of those papers were accepted by the editors despite the damning reviews. From the publishers on Beall's list that completed, mainly formal, review process, 82% accepted the paper (5).

The Beall's initiative and action spotted the publishers with poor quality control. Even though, the number of predatory publishers and predatory journals has continued to escalate at a rapid pace. Predatory journals are the most prevalent type of pseudo-journals estimated about 8000 active predatory journals, with total articles increasing from 53,000 in 2010 to 420,000 in 2014 (an estimated three-quarters of authors were from Asia and Africa) (1). The Beall's list expanded for the next five years to about 4,000 publishers and journals, which was nearly half of all open access journals included in the DOAJ database in 2016 (10,11).

Cabell's directory appeared a few years ago, which has its own newer criteria for a list of predatory journals. Jeffrey Beall has moved his list to Cabell's International di-

rectory as an updated and more organized version of the list of predatory publishers and blacklisted journals (12, 13).

#### 4. CAUSES AND CONSEQUENCES OF PREDATORY PUBLISHING

Two main factors contributed to the expansion of predatory publishing: a) the prevailing scientific ethos-imperative “publish or perish”, and b) the open access model adopted during the 1990s and expanded into the 21st century, with the fast Internet. Unfortunately, predatory publishing is often confused with open access publishing, whereby studies are free to all and can be reused for many purposes. Legitimate open access publishing—which has widely benefited scientific communication—uses all the professional and ethical practices associated with the best science publishing. Predatory publishing upholds few if any of the best practices yet demands payment for publishing. Under traditional models of publishing librarians were sophisticated purchasers of subscriptions, but in this new model many individual researchers are unable to distinguish between reputable and predatory publishers and journals (1, 14, 15).

A large number of young and novice researchers, along with several eminent researchers, actively and unethically use fake predatory journals to produce their CVs and bibliographies of publications, in order to recruit, fund more studies, grants, and even promote academic titles and careers. On the other hand, inexperienced researchers can become “victims” of these journals, first of all from low and middle income countries (14, 15).

There is a huge loss of funds and valuable resources of scientists and authors due to the high APC and guaranteed approval of manuscripts for publication in these journals without or with superficial review. The more articles in a predatory journal would be published quickly, the more money predatory publisher would make from authors in the form of high APC.

The validity of research and the quality of published articles are endangered because of lack of rigorous peer review process which is typically adopted-practiced by reputable indexed journals.

Published articles are of low quality and validity, in terms of consistency of objectives, methodology and data analysis, on the one hand, and results and discussion on the other, as well as inappropriate citation format (Vancouver and Harvard style or APA format), a lot of errors in text and false, plagiarized and distorted evidence with unreliable facts.

Loss of significant validated studies and valid papers due to publication in fake journals that could have been a breakthrough in research progress (16, 17).

Unfortunately, some fake journals do indeed permeate reliable sources and are indexed in reputable biomedical databases such as Pubmed, Pubmed Central, Medline, SCOPUS, and the Web of Science (16-18).

Beside predatory publishers there is a problem on the other side, too. Some researchers take the advantage with

unethical behavior for shortcuts and quick and easy publishing in predatory journals paying for the publication of plagiarized or self-plagiarized work. Unethical scientists, gaming the open access publishing system and ethics, are gaining future research funding and academic advancement, earning tenure and promotion at the expense of the honest scholars (1-3). The biggest consequence of predatory publishing is that tens of thousands of researchers have obtained master's and doctoral degrees, obtained academic titles, promotions and jobs, and this has led to a loss of credibility of academic profession, grading ratings and the educational value system (19).

## 5. EXAMPLES AND FREQUENCY OF PREDATORY PUBLISHERS AND JOURNALS

The OMICS International and the “Journal of Forensic Anthropology”, renamed in “Journal of Anthropology Reports” are the typical examples of predatory publisher and predatory journal (20). The journal was established in April 2016 and the first Editor-in-Chief was invited to be Izet Masic, accompanied with two Executive editors, Doncho Donev and Srecko Gajovic, without knowing the core of the problem in which they were involved. The e-mail correspondence with the person in charge, James Franklin, was strange and suspicious from the same beginning and the trapped editors discovered by Google searching how OMICS group operates. All mails, common and individual, with request for withdrawing the names of three editors were ignored by Mr. Franklin and he refused to respond to the messages of editors. In 2017, Professor Izet Masic published a paper on predatory publishing and experience with OMICS International (16) and his name was removed and replaced with another person, the current Editor-in-Chief, Ronn Johnson, Assoc. Professor at the School of Leadership and Educational Sciences, University of San Diego, U.S. Such name is not listed among the Faculty staff at the School in San Diego. The names of the Executive Editors are still present at the web-site of the Journal of Anthropology Reports, compromising their authority and reputation. The most severe attacks and blaming were extended by Mr. Leonid Schneider from Germany, the owner of the science journalism blog “For Better Science”.

The debate initiated by Jeffrey Beall is continuing in the scientific community with increased number of authors and published articles on this still unresolved issue in the last about 10 years. The frequency of predatory publishing is much higher in developing countries (in 2019, 81 authors from Vietnam published papers in predatory journals). Cress P. (2017) pointed out that 25% of all journals are predatory (21) and Wilkinson TA. (2019) estimated that they create an industry worth \$10.5 billion per year (22).

## 6. THE FEATURES AND CHARACTERISTICS OF FRAUDULENT OR FAKE JOURNALS

### 6.1. Infrastructure and web-site

There is a global distribution of predatory open access

publishers, editors, and bank accounts and most of them cloak their true geographic location. Predatory publishers create journals with “clone” names, as well as use a website name or design, which strongly resembles the Western academic publishers and prestigious journals even the locations revealed by IP addresses of editors and bank invoices might be in countries at other continents, first of all Asia (India, Pakistan, Turkey, China etc.), North and South America, Africa, Europe etc. For example, the American Journal of Medical and Dental Sciences and the European Journal of Chemistry are published from Pakistan and Turkey, respectively (5).

Below are presented some other features and characteristics of predatory, fraudulent or fake journals related to their Infrastructure and web-site (1, 15-18, 23-27):

- Predatory publishers mimic the design and structure of legitimate journals;
- “Hijacked journals” refer to the creation of a counterfeit website that mimic the website of a legitimate journals in order to solicit submissions and collecting author fees from authors who believe they are sending their work to the legitimate journal;
- They use fake-false journal impact factors (IF) and database inclusion or those features are not available;
- Procedures for handling manuscripts and journal workflows are unclear;
- There is no archiving of journal content or digital storage of published articles;
- Poor management of potential conflicts of interest, handling of errata, and transparency of journal processes, lack of withdrawal policies and practices including fees;
- False placement of the logo of the Committee on Publication Ethics (COPE) on the website of the journal, without really being a member of COPE;
- False “International Standard Serial Number” (ISSN) for OA journals and this cannot be checked in DOAJ and / or ROAD databases;
- False claim of indexing in various known databases such as PubMed, PubMed Central, Medline, SCOPUS and / or Web of Science;
- Published articles contain a lot of mistakes in grammar and spelling, data analysis, discussion of results due to little if any quality control and virtually no transparency about processes;
- Images and logos are unprofessional, distorted and blurry;
- The titles of predatory journals are somewhat close to the names of established registered journals and it isn't easy to be distinguished and considered fraudulent;
- Predatory journals use many strategies and techniques to show that they are reputable and to attract the interest of young naive researchers or those who would like to publish a paper very quickly in order to achieve their promotion;

- Most fake journals can be maintained by one person and one computer;

### 6.2. Approach towards authors and the scientific community

The main characteristics of the predatory publishers related to their attitude-behavior towards the potential authors and the scientific community are as follows (1, 19, 23, 24):

- Aggressive marketing for recruitment of articles via mass “suspicious-unsolicited” e-mails to large number of individuals, inviting potential authors to submit articles for upcoming editions or for special thematic issues, giving attractive promise for quick review and rapid open access publication for author fees that may be similar to those of legitimate author-pays journals. In some cases predatory publishers collect publication fees but the promised published articles never appear on the journal website;
- Sending invitation to scholars to participate as members of the editorial board or to be reviewers of the journal;
- Involving diligent scholars in the editorial board, with or without consent, and not allowing them to leave the editorial board;
- Bringing unqualified scientists to the editorial office (without ORCID ID and/or fake Researcher ID);
- Usually there is no possibility of online submission, but authors must send the manuscript by private e-mail;
- Low editorial standards of reporting which doesn't comply with agreed ethical guidelines and recommendations for research and publishing integrity;
- Do not provide proper peer review to identify “fake” papers;
- Fast acceptance of the manuscript (in less than 10 days) and quick publication (in a few weeks), without the procedure for quality control, without checking the manuscript for plagiarism and linguistic proofreading;
- Notice to the author for acceptance of an article for publication is very short, without any remarks and suggestions for improving the quality of the article, and with payment information, usually high fees for publication;
- The motive is financial gain and the amount of the publication fee APC is sometimes unclear and the amount can be negotiated if the author complains;
- Predatory journals reduce or eliminate services consuming editor and staff time for manuscript evaluation, peer review, editing, and quality assurance, skimming the author fees as profit.

### 7. HOW TO RAISE AWARENESS AND WARN SCIENTISTS TO AVOID THESE JOURNALS

Many authors pointed out the problem of predatory publishing and its consequences and emphasized the necessity of awareness rising and warn scholars, espe-

cially young researchers, how to recognize and avoid submission of their papers to predatory publishers and journals. Beall J, 2012, pointed out that “Scientific literacy must include the ability to recognize publishing fraud.” (2). Leading international associations concerned about research and publishing ethics provided guidance to help editors, researchers, funders, academic institutions and other stakeholders to distinguish predatory journals from legitimate open access journals, as well as for strengthening research and publishing integrity for overcoming correctable weaknesses in the design, conduct, and analysis of biomedical and public health research studies, which can produce misleading results and waste valuable resources (1, 2, 6-8, 14-16, 23-26, 28, 29):

- Raising awareness in the scientific community is necessary to distinguish reliable and valuable journals from predatory-fake ones, as well as avoiding and completely boycotting predatory journals.
- Continuing education, both of existing and emerging waves of scholars, must be the purpose and imperative of the academic community;
- To protect the review process as the heart of scientific publishing, the academic and scientific community must set criteria for scientific progress by not recognizing and not scoring articles published in predatory journals;
- Distinguish reliable and valuable journals from predatory ones, taking into account: publishing ethics, review process, international academic standards, indexing, storage in digital repositories, metrics and sustainability;
- Two substantial efforts to assist stakeholders in distinguishing predatory from legitimate journals before submitting a manuscript for publication, the author should check the ‘blacklists’, Beall’s Lists and Cabell’s Directory, but also carefully assess the characteristics of journals in journal registration databases (DOAJ, ROAD, COPE and ICMJE), as well as in reputable databases for indexing journals such as PubMed, PubMed Central, Medline, SCOPUS and / or Web of Science through its official websites;

### 8. CONCLUSION

Unaware of the detrimental effects associated with publishing in disreputable journals, inexperienced researchers can fall victim to predatory publishers and journals. So far the efforts are directed toward increasing awareness in the scientific community how to differentiate between trustworthy and reliable journals and predatory ones, as well as the authors and readers to avoid and completely boycott predatory journals. Continuous education of authors, both the existing and the newly-emerging wave of scholars, must be the purpose and the imperative of the academic community. At the individual level, both as readers and as authors, we should completely boycott and avoid potential predatory journals. Researchers should consider some of the above-men-

tioned proposed characteristics of predatory journals. By understanding how predatory publishers operate, researchers can avoid becoming victimized by them.

But the fight against predatory publishers is too great for individuals. In order to protect the peer review process as a heart of the scientific publishing, the academic and scientific community must set the criteria for scientific advancement by not recognizing and valuing the articles published in the predatory journals. Universities and governments should work together to establish precise criteria for grants, promotions, awards and other funding or evaluations, excluding papers published in predatory journals, establish information and staff orientation programs, master's and doctoral programs based on research and publishing integrity.

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# On Occasion of the 11th "Days of AMNuBiH 2020" and "SWEP 2020" Conferences, Sarajevo, Bosnia and Herzegovina

**IZET MASIC, ASIM KURJAK, MUHAREM ZILDZIC, OSMAN SINANOVIC, SEFIK HASUKIC, EMIR MUJANOVIC, SENAJD TRNACEVIC, SYLWIA UFNALSKA, MILAN STANOJEVIC, MIRO JAKOVLJEVIC, SLOBODAN M. JANKOVIC, DONCHO M. DONEV**

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In Sarajevo, Bosnia and Herzegovina, at Holiday hotel on November 14th, 2020 was organized 11th annual scientific meeting of the Academy of Health Sciences of Bosnia and Herzegovina "Days of AMNuBiH 2020" and 3rd Seminar about Writing, Editing and Publishing - "SWEP 2020".

Topics of the conferences were:

- Bosnia and Herzegovina experiences related to the COVID-19 pandemic;
- Study design and editing of medical journals.

Speakers at the conferences were from Bosnia and Herzegovina: Izet Masic, Sarajevo (Medical, Social and Ethical Dilemmas in COVID-19 Times: How to Decide Who and What to Do and The Basic Principles of Editing Biomedical Scientific Journals), Muharem Zildzic, Gracanica (The Importance of Nutrition in Boosting Immunity for Prevention and Treatment COVID-19), Osman Sinanovic, Tuzla (COVID-19 Pandemic: Psychiatric and Neurological Consequences), Sefik Hasukic, Tuzla (The Elective Diagnostic Laparoscopy in Chronic Abdominal Disorders in Pandemic Conditions), Senaid Trnacevic (Organ Transplantation in Bosnia and Herzegovina Within Limiting Circumstances Cased by COVID-19 Pandemic), and Emir Mujanovic (Organization of the Work of the Medical Institute Bayer in Tuzla During the COVID-10 Pandemic).

- from Croatia: Asim Kurjak, Dubrovnik (Has Science Helped or Hindered the Battle with the Corona Pandemic), with co-authors: Milan Stanojevic, Zagreb and Miro Jakovljevic, Zagreb.
- from Serbia: Slobodan Jankovic, Kragujevac (The Importance of Adequate Research Design in Biomedicine);
- from North Macedonia: Doncho Donev, Skopje (Predatory in Scientific Publication - a Burning Issue in Science); and
- from Poland: Sylwia Ufnalska, Poznan (Physical Activity Outdoors as an Alternative to Lockdown: the Three Cs Strategy).

During SWEP 2020 participants have possibility to at-

tend Short course in research design - five key components / phases:

1. Choice of research topic;
2. Choice of study type;
3. Sample size calculation and sample selection;
4. Selection of study variables;
5. Ethics Committee and regulations.

Presidency of the "Days of AMNuBiH 2020" and "SWEP 2020" were academicians: Izet Masic, President, and Mu-

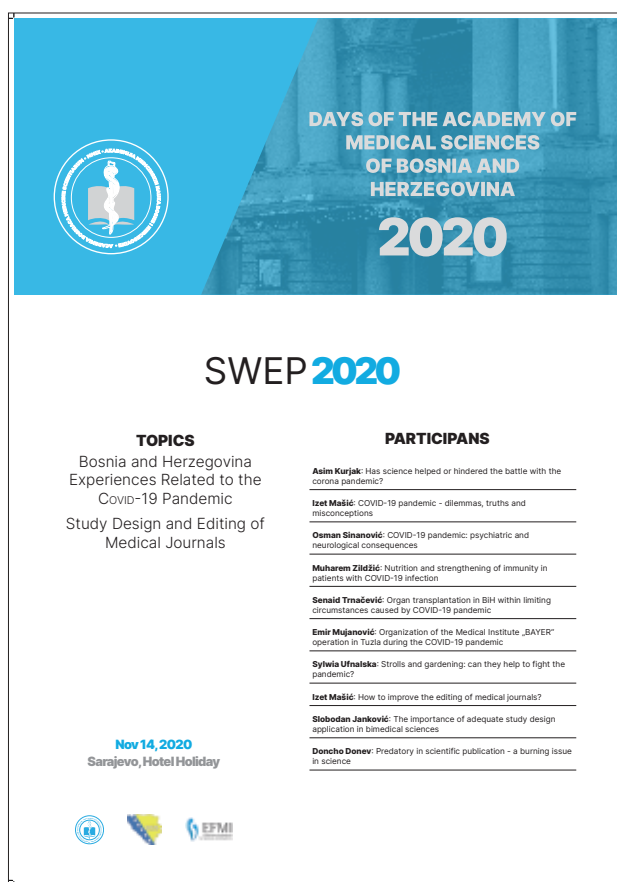


Figure 1. Poster of the "Days of AMNuBiH 2020 and SWEP 2020" held in Sarajevo on November 14th, 2020



Figure 2 Moderators of the "Days of AMNuBiH 2020 and SWEP 2020": Izet Masic, Slobodan Jankovic, Muharem Zildzic (from right to left)

Muharem Zildzic and Slobodan Jankovic, members, who excellently co-ordinated and administrated Webinar using Zoom ICT with participants in Dubrovnik (Asim Kurjak and Milan Stanojevic), Split (Izet Hozo), Skopje (Doncho Donev), Memphis (Kenan Arnautovic), Tuzla (Osman Sinanovic, Sefik Hasukic, Emir Mujanovic and Senaid Trnacevic), Sarajevo (Mirza Biscevic) and Gracanica (Nizama Salihefendic).

During "SWEP 2020" in Sarajevo members of AMNuBiH accepted as official strategic documents of Academy of Medical Sciences of Bosnia and Herzegovina: "The Basic Principles of Editing Biomedical Scientific Journals" and "Importance of Adequate Research Design in Biomedicine", as Guidelines which will be published in the next issue of *Acta Informatica Medica* journal and distributed to other medical journals in former Yugoslav countries, similarly we have done it at "SWEP 2016", when 17 editors of Medical journals from South Eastern Europe countries adopted "Sarajevo Declaration on Integrity and visibility of Scholarly Publications". This publication primarily was published in the *Croatian Medical Journal* and translated in several other languages..

The first document is useful for improving editing of medical journals, both on regional and global level, because numerous studies, editorials, expert opinions and other types of publications direct our attention to weaknesses and mistakes of editing that have or will have adverse consequences to ultimate goal of writing in health sciences. Just in one study of highly ranked orthopedic journals citation error rate of 41% was found, as we noticed during presentation of these Guidelines at "SWEP 2020". Editors of medical journals are faced with a number of problems that are mostly caused by ignorance or inexperience of the authors: duplicate submissions, inadequately prepared submissions, insufficient availability of competent and knowledgeable reviewers, low methodological quality of the submissions, etc. It is a reason that editors of medical journals are left without evidence-based practical guidelines how to conduct their job with success and avoid many pitfalls in their way.

The second document used an analytical method for explanation of five most important steps and phases which are obligatory to use in the process of making of appropriate and qualitative research design for providing study investigation in biomedical research. It will be very useful for validity of a study results depends directly on appropriateness of its design, because it is only through careful planning that bias is minimized and the aims set in advance achieved. If all five essential steps are thoroughly completed, as described in this document, the study that was designed will be most likely free of critical methodological errors.

Finally, this our annual meeting was organized in very bad and difficult Corona time, when almost 1000 citizens of Bosnia and Herzegovina daily suffered by COVID-19 infection. Unfortunately, schools, faculties, universities, libraries, other important institutions and educational and social associations are closed. We are happy that our Academy didn't break our activity and its members at the "Days of AMNuBiH 2020" and "SWEP 2020" conferences in Sarajevo have given a small contribution to medical science for continuing the fight with corona virus.



Figure 3. Academician Asim Kurjak presented his paper via Zoom from Dubrovnik, Croatia



Figure 4. Academician Doncho Donev presented his paper via Zoom from Skopje, North Macedonia

# BOSNIAN AND HERZEGOVINIAN EXPERIENCES RELATED TO THE COVID-19 PANDEMIC

## ABSTRACTS

### Has Science Helped or Hindered the Battle with the Corona Pandemic?

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#### ABSTRACT

The coronavirus pandemic exposes the weaknesses of globalization and serves as a warning on the constants of the natural law on the survival of any nation or human community: only a well-organized modern state is capable of protecting its citizens, and this presumes the acceptance of the roles of borders, control and the authority principle while the economic and healthcare sovereignty requires the necessity of the principle of self-sufficiency in the areas of agriculture, nutrition and the necessary production of medication and primary products for the needs of the populace. Taking into account everything we have learned about the SARS-CoV-2 virus so far it comes as a surprise that there hasn't been a more intense scientific debate on whether the blind lockdown model, implemented by most national governments, was truly an appropriate response to the challenges posed by the pandemic (1, 2). Today, when we know more about the transmission modes of SARS-CoV-2 (primary mode is by respiratory droplets) as well as how dangerous it truly is (much less than previously thought), it is time to reassess the first radical epidemiological reactions (3, 4, 7). This needs to be done not to accuse someone of mistakes, but in order to plan future action. It is clear that in the beginning numerous countries opted for radical epidemiological measures because we didn't have enough information about the COVID-19 pandemic but now the time has come to ask the questions about the weirdly mingled responsibility of politicians and epidemiologists who persist in scaring the populace with threats of the virus without considering the general consequences (5, 6, 7). Individuals who bravely provoke the world scientific community by in-

sisting on a discussion based on data and not assumptions are actually very rare.

**Keywords:** coronavirus pandemic, human community, epidemiological measures.

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### Medical, Social and Ethical Dilemmas in COVID-19 Times: How to Decide Who and What to Do?

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#### ABSTRACT

**Background and Objective:** After almost of one year when the first case of COVID-10 infection was discovered and recorded in Wuhan Province in China, Pandemic of



COVID-19 is still full of prejudices and dilemmas (1). No one serious Evidence Based Study in the scientific literature has been described. Author of this article was one of the first 100 authors in the world which paper was deposited in PubMed database in March of the 2020 (1). Currently in PubMed are deposited more than 5000 papers with subject of COVID-19 published in journals in almost every country in the world by authors from almost every medical and submedical disciplines. Everyday in the world somebody organizing some Special Topic Conference, mostly as webinars, within the every scientific medical field where biomedical scientists and experts trying to contribute with scientific and important facts and experiences, according pandemic of COVID-19 infection and possible solutions how to stop consequences of the pandemic globally. Unfortunately, all measures proposed by experts of World Health Organization (WHO) and Regional and National Scientific and Public Health Institutions in the world are not enough effective (2-5). Till now number of infected and died people caused by COVID-19 is more than 50 million cases. Author's of this paper written in February this year and published in *Materia Socio-Medica* journal about three dilemmas are still active, better to say, much more intensive than 6 months ago (1).

**Methods:** This review has descriptive character with intention to summarize current important facts about COVID-19 pandemic and most important dilemmas described in scientific literature until today.

**Results and Discussion:** The novel coronavirus (COVID-19) pandemic day by day raising with more and more medical ethics dilemmas. In a pandemic conditions public health institutions (like Ministry of Health, Public Health Institute) have responsibilities and considering who and when drive decisions on prioritizing who is or will be tested for COVID-19 disease (dilemma 1 in Bosnia and Herzegovina). Rationing as the supply of key resources such as ventilators has been outstripped by the number of hospitalized COVID-19 patients (dilemma 2 in Bosnia and Herzegovina). The severest form of COVID-19 includes pneumonia, which can require admission to an highest healthcare protection institutions, like University Clinical Centers or Cantonal hospitals for mechanical ventilation. Medical (COVID-19 ambulances/surgeries, medical staff (physicians, nurses, etc.), corona tests, etc) utility based on scientific patient profiles should guide decisions to ration critical care resources such as ventilators.

Described experiences in the scientific literature, as current most important dilemma, regarding COVID-19 pandemic are (2): a) **Treatment:** In all countries in the world caring for the anticipated surge of seriously ill COVID-19 patients is likely to involve heart-wrenching decisions for healthcare professionals. The first step in managing critical care resources is screening out patients who are unlikely to need critical care and urging them to self-quarantine at home; b) **Testing:** There has been rationing of COVID-19 testing since the first novel coronavirus patient was diagnosed and the primary purpose of testing

during a pandemic is advancing public health (purpose of the test is pure public health epidemiology keeping track of who has COVID-19 in service of trying to limit the spread of the disease to other people). In that case the prioritization isn't so much about who is at greatest risk, and who is more likely to interact with lots of people, or to have interacted with more other people; c) **Healthcare professionals (family physicians, infectologists, epidemiologists, medical nurses, patronage nurses, and other health workers):** The COVID-19 pandemic involves competing obligations for medical professionals. They have a set of obligations that inclines them to go to work when they get the call. On other side they, also, have own interests, don't want to get sick working at risk places with possibly already infected patients. And, they can incline them not to work. The punchline is there is an ethical consensus that they have a prima facie duty to work because of everything that has been invested in them (2), because of their unique position where not just anybody can replace them, Community/society looks to them to serve this function, and because they went into this profession and are expected to go into work. The obligation of medical professionals to show up for their jobs is not absolute (2). If hospitals don't have personal protective equipment, they are in no position to tell their staff to show up and work. If a hospital cannot provide even a basic level of safety for their employees to do their job, then they are turning their hospital not into a place to treat patients; d) **Vaccine:** Vaccine against COVID-19 is still in phases of testing and not available yet for official and large treatment (8). But when becomes available, Governmental bodies, healthcare decision makers, public health officials, and healthcare providers will face rationing decisions until there is sufficient supply to treat population. The question is, when the vaccine comes out, who will be in the first group: a) to want to prioritize are healthcare workers, who are at risk of getting infected by doing their jobs and saving lives; b) to want to prioritize people who serve essential functions to keep society going—the people who keep the water running, the lights on, police, and firefighters; c) to want to start looking at the high-risk groups (old people, patients with chronic diseases, etc) (1, 8).

Scientists who are interesting with health ethics speaking (Cheney K, 2020 (3), Bustan S. et al., 2020 (2)); about most important ethical dilemmas: a) **Responsibility:** Can medical responsibility change in times of pandemic? b) **Fairness:** In times of emergency, scarce healthcare resources, and risk of infection to the medical staff, how do we decide where we draw the line of whom we treat, who will live and who will die and how to ration treatment without denying care (triaging resources)? c) **Dignity:** Does the need for increased awareness of public harm in a pandemic justify impinging on patients' rights to bodily and personal dignity and privacy? d) **Honouring death:** Does public interest in social distancing outweigh the patient's right not to die alone and the family's right to be with their dying relative? (3, 4).



The challenging questions raised here are intended to reinforce our ethical values and speak of the well-being of the sick human being, the dignity of the dead person, and refer to a patient as a person to be cared for rather than a critical case or a contaminating agent. And while the coronavirus continues to widely spread across the globe, we hope that our discussion can serve as a resource for advanced care planning, helping medical providers and other specialists to consider the shared important aspects of medical ethics in times of great uncertainty.

Neves N. et al. written the text with interesting approach: *Ethical dilemmas in COVID-19 times: how to decide who lives and who dies?* (6), and they noticed that the pandemic reduction was not a priority for the US government, and many other opulent countries did not prepare adequately for it, so that the enormous responsibility to confront it befell on the medical providers. This imposed on them an uneven focus on present day patients, rather than the actual and prospectively sick. If we speak of fairness, we state that reducing the pandemic risk is a global public good inscribed in a complex temporality. a) Who gets healthcare resources? b) Can it be based on meritocracy, age, or function? c) Can we apply the same principles to all COVID-19 and non-COVID-19 patients? d) How to prioritize access to healthcare? (6). But during a pandemic, which is a natural and societal threat, we are facing the fact that rules can be consistent only if the context of disruptions of my narrative representations, my narrative world, can remain a consistent world as well.

From an ethical perspective, it can be argued that value judgment is an attempt of judgment based on a careful evaluation of the information available, taken as incomplete and evolving. It is worth exemplifying a value judgment on how to proceed in a medical emergency. In this case, the quality of judgment is incomplete since it is the result of cultural or personal limitations. Valuation is essential as an element for the contextualization of ethics in its broadest sense. Ethics is shaped based on the ingraining of values in subjects and the society in which they are inserted, and, from this set, each one proposes their actions. That being said, it is necessary to value to intervene. It is worth noting that the medical field assigns a different value to life, according to age, providing distinct care to children, adults, and the elderly. From this perspective, the ethical values necessary to ration healthcare resources in an epidemic have high prestige and can converge into some proposals based on fundamental values, such as maximizing the benefits produced by scarce resources, treating people equitably, promoting and recommending instrumental values, and giving priority to critical situations. A recently published article taking into account the ethical particularities mentioned produced specific recommendations to allocate medical resources in the COVID-19 pandemic proposed by Neves N, and associates (8) are: "a) Maximize benefits—the priority of limited resources should aim at saving as many lives as possible and maximizing improvements throughout life post-treatment. This premise is consistent both in the

perspective of utilitarian and non-utilitarian ethics; b) Prioritize health professionals—resources such as tests, PPE, ICU beds, ventilators, therapeutics, and vaccines should be directed initially to healthcare professionals, particularly those who face a high risk of infection and whose training makes them difficult to replace, which can cause insufficient assistance and, as a result, an increased number of deaths due to the decreased number of trained professionals; c) Do not allocate based on the order of arrival—in case of patients with a similar prognosis, the operationalization should be random. Prioritizing those who arrived first would be unfair; d) Be sensitive to the scientific evidence—protocols must follow scientific guidelines and be updated as they develop; e) Reward research participants—people who participate in research to prove the safety and effectiveness of vaccines and therapeutic measures should receive some priority in interventions; and f) Apply the same principles to all COVID-19 and non-COVID-19 patients—the fair allocation of resources that prioritizes the value of maximizing benefits applies to all patients who need them" (8).

It is necessary to implement policies of rationing in order to balance multiple ethical values. Naturally, there will be different judgments in different circumstances, but it is essential to maintain transparency to ensure public trust. It is possible to draw up prioritization guidelines using well-established ethical values and recommendations to achieve fair procedures for resource allocation. That way, it is possible to prevent individual physicians from being faced with the grim task of improvising.

The goal with clinical ethics support is to enable clinicians and health service decision-makers to think more clearly about complex ethical questions...

**Conclusion:** The pandemic or epidemic of COVID-19, unlike all previous epidemics or pandemics in the recent history of medicine (1), has brought many controversies about which the future and its actors in several scientific fields of interest will provide relevant observations, opinions and conclusions. Among other things, there is controversy regarding vaccines and vaccinations against Corona infections (9). But there are many other controversies and doubts which relate to life, work, health in general and the health systems and its subsystems, and are responsible for ensuring the work, as well as, all other activities of the individual and the community. In the use and misuse of all types of information, and they are mostly health information, the autocratic manner of dealing with decisions at all levels in the health care system (but also in society and politics in general) came to the fore, which fundamentally „transformed“ the normal system functioning - from local levels in Family Medicine units to those at the tertiary and quaternary level, where the hypertrophy of COVID-19 and its consequences „distorted“ the health system into forms that are not seen even in the most specific conditions, the so-called extraordinary conditions, such as states of war and catastrophic natural disasters. This prompted the authors of this article to emphasize the significance and importance

of the phenomenon of fear for life or fear of death, which, among other things, has intensified precisely with what has been said in the previous text. We should especially emphasize the ethical moment related to all information about COVID-19, which „kills“ us every day and produces fear tendentiously, irresponsibly, but also out of ignorance, which has not been a mass phenomenon so far. Every news in the media, television shows, from current daily news to educational content, on social networks has partial characteristics of unethical and immoral behavior - data on individuals, text and photographs were published, which in codes of ethics and declarations of rights and charters have the character of violations and bear the traces of criminal liability. Legal experts, lawyers and other law enforcement experts are already being called to file lawsuits and criminal charges for the health consequences of COVID-19 for individuals and their families, from the unnecessary wearing of masks, irrational purchase of food and medicine and the creation of unnecessary piling of supplies in homes, preventing regular control, diagnostic and therapeutic procedures at higher levels of health care, denying various physical rehabilitation procedures and treatments, especially to the elderly, who were and will be the primary risk group and potentially most at risk of COVID-19.

“The phenomenon of fear is otherwise present in this category of the population, due to those conditions and diseases from which they otherwise suffer, and which occurred both physiologically and pathophysiologically with age. COVID-19 and this kind of relationship that this text write about only intensified that fear even more. Perhaps this is one of the „determining tendencies“ of the COVID-19 project, as psychiatrists would point it out, and which will be one of the important topics for future research” (9). The term PCSS (Post Corona-virus Stress Syndrome) which I proposed to be used for consequences of “corona time” several months ago every day is stronger and stronger, Reason way even common peoples know (1).

**Keywords: COVID-19, prejudices, dilemmas, vaccine.**

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## The Importance of Nutrition in Boosting Immunity for Prevention and Treatment COVID-19

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#### ABSTRACT

**Background:** Life and health directly depend on food and normal digestive system functions, as well as eating habits. Absorbed essential and beneficial nutrients from food are used by all human organic systems to maintain their functions for the purpose of maintaining health. The immune system resists harmful agents from the environment, such as viruses and bacteria, by raising the level of its activity during infection. Such activity requires an accelerated metabolism. Increased metabolic activity requires more intense energy sources and specific substrates for biosynthesis of regulatory molecules and activation of cellular and biochemical elements of immune defense. Adequate food choices and a wide range of nutrients are necessary to maintain optimal immune system function, and this is a prerequisite for an adequate response to prevent more severe clinical forms of COVID-19 disease. In the fight against the COVID-19 pandemic, little attention is paid to strengthening the natural abilities of the human body and its immune system to prevent entrance of the human SARS-CoV-2 virus, and to prevent its replication in the vital organs cells. There is scientific evidence that lifestyle and diet modification with nutritional interventions can strengthen the immune system and thus prevent and mitigate the pandemic spread of this disease. **Objectives:** The goal of this article is to evaluate new findings on the impact of food, specific nutrients and eating habits on immune system function during the COVID-19 pandemic. **Methods:** The available literature was analyzed using the key words: food, immune system, COVID-19, and the results of studies that have scientific evidence (EBM) for the positive impact of food on the activity of the immune system during this disease were summarized. **Results and Discussion:** Food, diet and digestive function play the most important role in the overall immune response to viral infections. It

has been proven that the active ingredients of food can strengthen or weaken the immune system (immunomodulation or immunosuppression). In addition to providing energy needs in preserving life and health, food also has an emotional, psychological and social function. The psychological, social and emotional function of food can directly affect the control of stress, stabilization of the emotional and psychological state of the patient, which is an important factor for maintaining a stable immune system. Some food ingredients destroy or inhibit various microorganisms in direct contact. This action is performed by destroying the phospholipid membrane, inhibiting enzymatic reactions or acting on the genetic structure of microorganisms. Another way is to act through the immune system and various biochemical mechanisms. Dietary supplements are often used to boost immunity. The needs for food supplements should be individualized and harmonized with the immunomodulatory properties of individual products, and the assessment of the nutritional status of the consumer. Organic balanced food adapted to each person (personal diet) is the first condition for creating an adequate natural defense system. An adequate immune response, regardless of food choice, depends on food consumption habits and control of all 5 functional stages of digestion. Each of these phases is controlled with the nervous system of the digestive tract and the brain. Any disorder in this whole process can lead to metabolic disorders, insulin resistance, diabetes and other immune autoimmune diseases. Such disorders weaken the immune response to viral infections, so an increased incidence of COVID-19 has already been proven in persons with increased weight, hypertension, diabetes and autoimmune diseases. The strongest natural first line defense is the healthy mucosa of the initial parts of the respiratory and digestive systems. Eyelashes and mucus on the surface contain substances such as lysosome and antibodies from the IgA group. The mucus also contains glycoproteins - mucins that can bind viruses to their structure by imitating ACE receptors and remove them from the body in the form of mucus. These mucosal immune structures depend on the adherence of important food ingredients such as vitamins, minerals, proteins, and essential fatty acids. Disorders in the immune function of the intestines and microbiome were registered during the COVID-19 pandemic. There are studies that recommend the standard use of prebiotics and probiotics in the prevention and treatment of COVID-19 disease. Some probiotic cultures have the ability to act in the ACE receptor region by inhibiting virus entry into cells. A link between lung microbiome and gastrointestinal tract with a synergistic immune response and prevention of bacterial lung superinfection has also been demonstrated. There are indications that the COVID-19 pandemic also came as a result of the weakening of the immune system of the entire human race due to changes in diet that occurred in the 21<sup>st</sup> century. Until 50 years ago, man ate mostly organic food without additives. The current global characteristic of the diet is that food is produced in conditions

of contaminated soil, air and water. Food is taken in supermarkets, mostly industrially ultraprocessed and with many additives, preservatives and sugars. Genetically modified food directly impair the human DNA genome and has a direct negative impact on the function of the immune system. The consequences of such a diet are today's pandemics of obesity, insulin resistance, metabolic syndrome, diabetes and other chronic non-communicable diseases, which have greater destructive powers for human life than the SARS-CoV-2 virus itself. Food antioxidants control DNA transcription, cytokine production and secretion, and cell vitality. Phenols and carotenoids from food, which are most often antioxidants, can act on the regulation of all functions of the immune system. **Conclusion:** There are many types of foods that can affect the immune system in the human body, for which proven facts exist (EBM). Examples are: vitamins A, B, C, D and E, minerals selenium, zinc, iron and copper, omega 3 fatty acids, salicylates, carotenoids, polyphenols, flavonoids, glycosides and alkaloids. They have specific pharmacological effects in human health such as antimicrobial, antioxidant, anti-inflammatory and immunomodulatory. Some food nutrients are very valuable in maintaining a healthy immune system, and can be found in everyday foods, such as sea fish, berries, leafy vegetables, legumes, bee products, mushrooms, algae, herbs and spices. There is also evidence that this approach to nutrition can prevent COVID-19 disease or alleviate its clinical course, and accelerate the process of creating and maintaining specific immunity.

**Keywords:** Nutrition, immunity, COVID-19.

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### COVID-19 Pandemic: Psychiatric and Neurological Consequences

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## ABSTRACT

**Background:** Infection with the new corona virus (SARS-CoV-2) was first registered in December 2019 in China, and then later spread rapidly to the rest of the world. On December 31, 2019, the World Health Organization (WHO) informed the public for the first time about causes of pneumonnia of unknown origin, in the city of Wuhan (Hubei Province, China), in people who were epidemiologically linked to a seafood and wet animal whole sale local market in Wuhan. Coronavrus disease, called COVID-19 (Corona virus disease 2019), after China quickly spread to most countries in the wold, and the WHO on March 11, 2020 declared a pandmic with this virus (1). In Bosnia and Herzegovina, the first infected infected person was registered on 5.3.2020 in Banja Luka, and in the Federation of Bosnia and Herzegovina on March 9, 2020 in Konjic. Aim: To present some of psychiatric and neurological consequences of infection related to the SARS-CoV-2. Methods: Article has an analytical character and review of literature. Results and Discussion: SARS-CoV-2, has a high level of sequential similarities to the SARS-CoV-1 and uses the same receptors when it enters the human body (angiotensin-converting enzyme 2/ACE2)(2). COVID-19 is respiratory infection that is primarily transmitted via respiratory droplets. Typical symptoms of COVID-19 infection can be very moderate (infected can be even asymptomatic) to very severe, with severe respiratory symptoms (bilateral severe pneumonia), septic schock, and fatal outcome. COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2, in a number of patients also penetrates the CNS, and apparently could be responsible for fatal outcome in some cases (3,4-5). Experiments on mice have demonstrated that SARS-CoV probably enters the brain via the olfactory bulb, and then spreads to other specific parts of the brain such as the thalamus and brainstem through the olfactory nerves. Furthermore, there is evidence that coronaviruses attack peripheral nerve endings and reach the CNS via nerve synapses (4). The entry of the virus into the brain can lead to neurological and psychiatric manifestationss, which are not uncommon, including headache, anosmia, ageusia, encephalopathy, encephalitis, paresthesia, myalgia, Guillain-Barre syndrome, impaired consciousness, confusion or delirum and cerebrovascular diseases (3, 6). Due to the fact that iformation about the diseas caused by SARS-CoV-2 (COVID-19) spread very quickly, becoming pandemic even before the virus pandemia (infodemia), and after the disease spread outside China, confirming the remarks that it is very contagious disease, but also a fatal disease, the general public has become very upset (7-8). Psychosocial consequences as well as consequences for mental health are significant, both for the general population and especially for health workers of all profiles. Covid-19 pandemic is associaed with negative psychoso-

cial outcomes, including depressive sympotms, anxiety, anger and stress, PTSD, social isolation, loneliness and stigmatization (3, 9-10). Conclusion: The consequences of this pandemic on the overall life of people on the planet are significant and unthinkable. COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2, the RNA virus that causes the disease, in a number of patients also penetrates the CNS, leading to serious neurological disorders, and apparently it is also responsible for mortality. The entry of the virus into the brain can lead to neurological and psychiatric manifestationss, which are not uncommon including headache, anosmia, ageusia, encephalopathy, encephalitis, paresthesia, myalgia, Guillain-Barre syndrome, impaired consciousness, confusion or delirum and cerebrovascular diseases. Psychosocial consequences as well as consequences for mental health are also significant, both for the general population and especially for health workers of all profiles.

**Keywords:** COVID-19, Neurological disorders, Psychiatric consequences.

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## Organ Transplantation in Bosnia and Herzegovina Within Limiting Circumstances Caused by COVID-19 Pandemic.

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### ABSTRACT

**Introduction:** Organ transplantation at the time of the COVID-19 pandemic is very difficult to realize in all aspects of this method of treatment. Difficult communication, limited possibilities of diagnosis and accommodation, treatment and monitoring of patients-special conditions and procedures for testing, processing and treating patients have been created. **Objective:** The aim of the study is to analyze and describe the current situation about organ transplantation in Bosnia and Herzegovina, regarding limited conditions caused by COVID-19 pandemic and to propose adequate measures to solve the current problems. **Methods:** Data on the status of the transplantation program from the European Register of ERA-ADTA as a special contribution from 36 European countries and 17 other countries associated with ERA-EDTA was analyzed. Data from the Renal Registry of the Association for Nephrology, Dialysis and Transplantation in Bosnia and Herzegovina was also collected. the latest data on dialysis and transplant patients at the end of September 2020. A special organizational problem of organ transplantation in our country was pointed out. The Ministry of Health of the Federation of Bosnia and Herzegovina has prescribed the conditions and ordered the continuation of the transplantation process in the conditions of the Covid-19 pandemic beginning of May 2020. **Results:** The total number of transplants was reduced in the period from March to the end of September 2020, according to the official registers of transplantation centers in Eurotransplant. No organ transplants were performed in Bosnia and Herzegovina at that time. Forty dialysis patients who tested positive for Covid-19 from all over Bosnia and Herzegovina were monitored. Of that number, 5 died. In the time when there was no pandemic, there were no donors in our country with proven brain death in three years period before the start of pandemic, and therefore no organ transplantations were performed. Numerous in field procedures are needed to improve, mainly by educating the population about the importance of transplantation, medical workers, and the medical authorities that are most responsible. The donor network in Bosnia

and Herzegovina is significantly more active in assisting transplantation in our country in comparison to other countries. Organ transplantation should have a state priority and harmonized procedures between all levels of government. At present, there is no co-operation in this process between different levels of government, and Bosnia and Herzegovina does not have a single joint body or commission to deal with all aspects of this process. Republika Srpska and the Brcko District of Bosnia and Herzegovina do not even have a waiting list for patients who may receive organs with proven brain death. The waiting list in the Federation of Bosnia and Herzegovina includes 242 patients for kidney, 30 for liver and 12 for heart transplantation. **Conclusion:** The number of organ transplants in all European countries in the context of the Covid-19 pandemic has been significantly reduced. No organ transplantation were performed in Bosnia and Herzegovina since March. The transplant process must continue according to new procedures and is based on testings for Covid-19 infection.

**Keywords:** kidney transplantation, Covid-19 pandemic, ERA-EDTA Renal Registry.

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## The Elective Diagnostic Laparoscopy in Chronic Abdominal Disorders in Pandemic Conditions

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## ABSTRACT

**Background:** The first diagnostic laparoscopy on humans was performed in 1910. Initially, this method was mainly used by gastroenterologists. Since 1980, after the first laparoscopic surgeries, such as appendectomy, cholecystectomy, etc., surgeons have taken a leading role in the application of diagnostic laparoscopy (1-3). **Objective:** Indications for elective diagnostic laparoscopy can be divided into two basic groups: indications due to benign pathological conditions in the abdomen and indications due to malignant tumors, for biopsy and determination of their clinical stage as a prerequisite for proper therapy (4-6). In this study, we evaluated the use of elective diagnostic laparoscopy in our patients with chronic abdominal diseases and its importance in the proper treatment of patients. **Methods:** We analyzed patients who were admitted to the Surgery Clinic in the period 2015-2019 for elective diagnostic laparoscopy due to chronic abdominal diseases. It was not possible to diagnose the disease with other diagnostic tests. All patients were examined and all available diagnostic processing was performed. The decision for diagnostic laparoscopy was made at the Council for Digestive Diseases. **Results:** A definitive diagnosis was made in all patients who underwent diagnostic laparoscopy. In patients with chronic pain, it was most often chronic appendicitis, and appendectomy was performed in these patients. In all oncology patients, a tumor fragment was taken for definitive pathohistological analysis. Based on the definitive pathohistological analysis, further treatment of the patients was determined. In half of the patients, the diagnostic laparoscopy was at the same time therapeutic and was performed with the definitive treatment of the patient. **Discussion:** Diagnostic laparoscopy plays a significant role in the evaluation of chronic abdominal pain, especially in lower right quadrant pain in young patients (6, 7) In oncology patients with intra-abdominal tumors, preoperative diagnostic laparoscopy is often indicated to assess tumor operability (6-8). During diagnostic laparoscopy, it is possible to take a tumor biopsy directly under the control of a laparoscope, it is possible to take ascites for cytological processing, or to do peritoneal lavage and process the contents cytologically (6, 7, 9-11). In the hands of an experienced laparoscopist, diagnostic laparoscopy is a safe method for making a diagnosis. Its advantages are that it can be immediately therapeutic and the problem can definitely be solved (5, 6, 10).

**Key words:** diagnostic laparoscopy, chronic abdominal disorders.

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## Organization of the work of the Medical Institute Bayer in Tuzla during the COVID-19 pandemic

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## ABSTRACT

Medical Institute Bayer is a continuation of the BH Heart Center Tuzla, which was founded in 2008. The goal of establishing the Center was to build a modern, functional hospital that will meet all prescribed norms and standards, and eliminate all limiting factors in the development of cardiac surgery, interventional cardiology and vascular surgery. As part of the development of the Center and the new concept of operation, and in order to cover all new disciplines as well as those that will be developed in the future, in January 2020 the name of the institution was changed to Medical Institute Bayer - MIB. MIB was named after Dr. Karel Bayer, one of the most important figures in the field of medicine and the first president of the Association of Physicians of BiH in 1909. The first contact of the MIB with the coronavirus pandemic was recorded at the end of March this year with one of the employees. Shortly afterwards, 7 new cases were recorded, after which the MIB was placed in a state of iso-



lation, both for the patients and the employee. After the MIB was emptied, the rehabilitation of the facility began, which included measures of intensified disinfection of the entire institution, all rooms, all vehicles of the center and access roads, after which the MIB was put in a state of so-called "vacation facility", lasting 15 days. All MIB employees were tested for COVID-19 before re-entering the facility. Employees who entered the MIB after testing, were required to have personal protective equipment (mask, gloves, etc.) and all in accordance with the recommendations. Upon entering the Institution, they crossed the disinfection barrier and disinfected their hands with a disinfectant placed at the entrance to the Institution. Patients with symptoms of the underlying disease, before arriving at the MIB with the necessary medical documentation, are required to provide evidence that they have been tested for COVID-19 infection. Prior to patient entry, authorized staff at the triage point perform patient triage measures, complete an epidemiological form for each patient, and measure body temperature. The patient who then enters the MIB is obliged to have personal protective equipment (mask, gloves, socks). COVID-19 positive patients are treated as life-threatening-extremely urgent patients (since there is no possibility of testing). From entering the Institution to leaving it, it is obligatory to act according to the Protocols for the treatment of COVID-19 positive patients. If COVID-19 infection is confirmed in these patients, those patients are transferred to the so-called COVID ward, after which preventive intensive disinfection of the rooms in which the patient stayed is performed. The protection of staff is clearly defined by a special protocol for the admission and treatment of patients during a pandemic, which clearly defines the necessary protective equipment, rules for dressing and undressing, as well as rules for working in special conditions such as operating rooms.

**Keywords:** Medical Institute Bayer, COVID-19 pandemic.

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## Physical Activity Outdoors as an Alternative to Lockdown: the Three Cs Strategy

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#### ABSTRACT

**Background and Objective:** The focus of the COVID-19 pandemic is on protection of physical health, but its influence on mental health may in the future prove to be an even greater challenge for public health globally, as rightly emphasized in March by Masic et al. in *Medical Archives* (1). Mental problems are aggravated due to the enormous stress and anxiety caused by the pandemic itself, but also to the progressing restrictions, leading to lockdown in many countries. The Great Barrington Declaration (2), signed by many experts, draws attention to the devastating short- and long-term effects of the lockdown policy, especially in the most disadvantaged groups. Its signatories advocate Focused Protection, where senior citizens and other high-risk groups are strongly protected, but all the others resume life as normal. The Declaration, however, was criticized by some other health professionals (3), who argued that controlling community spread of COVID-19 is necessary. I have attempted to develop an alternative coronavirus strategy that could be a golden mean between the two opposing views. In my opinion, a major problem now is that lockdown, which forces many people to stay at home with their families most of the time, is – paradoxically – against the official advice for the public issued by the World Health Organization (4). One of the main WHO recommendations is to avoid the 3Cs: spaces that are closed, crowded or involve close contact (6-12). The "stay home" policy seems necessary to decision-makers, but I am afraid that it may bring opposite results now, because lockdown in autumn and winter is likely to facilitate disease transmission among family members more strongly than in spring, due to poor ventilation. **Results and Discussion:** Summary and further reading: 1. Editor of EASE Guidelines for Authors and Translators of Scientific Articles to be Published in English [www.ease.org.uk/publications/author-guidelines](http://www.ease.org.uk/publications/author-guidelines), Bosnian translation by Prof. Izet Mašić: [https://www.ease.org.uk/wp-content/uploads/2018/11/doi.10.20316.ESE\\_2018.44.e1.bos\\_.pdf](https://www.ease.org.uk/wp-content/uploads/2018/11/doi.10.20316.ESE_2018.44.e1.bos_.pdf) 2. Campaign "Help scientists save time for research" thanks to simplification of editorial requirements for initial manuscript submission <https://ese-bookshelf.blogspot.com/2020/10/ease-council-post-sylwia-ufnalska-on.html> 3. Outcome of lockdowns: "Basic epidemiological theory indicates that lockdowns do not reduce the total number of cases in the long run and have never in history led to the eradication of a

disease. At best, lockdowns delay the increase of cases for a finite period and at great cost." Comment to Great Barrington Declaration <https://gbdeclaration.org/frequently-asked-questions/> 4. Physical activity outdoors as an alternative to lockdown: the Three Cs Strategy. *Medical Archives* 2020 Oct; 74(5): 399-402. <https://www.ejmanager.com/mnstemps/10/10-1604859731.pdf?t=1604903670>, doi: 10.5455/medarh.2020.74.399-402 "The suggested solutions – eg encouraging regular physical activity outdoors (also for symptomless quarantined people), frequent ventilation with fresh air, and more careful use of antipyretics – can markedly help to reduce the rate of transmission of this disease. The new strategy is also likely to lower the risk of mental disorders and various diseases, thanks to promotion of a healthy lifestyle." 5. Strolls as a form of relax and disease prevention: German book "Body2Brain" (Kösel-Verlag) by Claudia Croos-Müller, a neurologist and psychotherapist. See also videos (in German): <https://www.youtube.com/watch?v=K2gGRvzRpV0> and <https://www.rfo.de/mediathek/video/der-body2brain-weg-mit-dr-claudia-croos-mueller/> 6. Health benefits of amateur gardening: "reductions in depression, anxiety, and body mass index, as well as increases in life satisfaction, quality of life, and sense of community" according to Masashi Soga, Kevin J. Gaston, Yuichi Yamaura. 2017. Gardening is beneficial for health: a meta-analysis, *Preventive Medicine Reports* 5: 92–99, <https://doi.org/10.1016/j.pmedr.2016.11.007> Moreover, gardening in cities (community gardens, also on rooftops, increasing permeable surfaces for better tree growth, etc.) can help to increase water retention and improve urban climate, see eg <http://vikalpsangam.org/article/nature-to-reign-in-floods-in-gorakhpur/#.X63Z9d5KiM8> 7. Flora of cemeteries: eg <https://www.researchgate.net/scientific-contributions/Aneta-Czarna-2041166206> 8. Respect for nature, need for biodiversity preservation. Visually about biggest threats to biodiversity: <https://www.visualcapitalist.com/biggest-threats-to-earths-biodiversity/?fbclid=IwAR1GDcP1p6mZVBSiulino5wppnLDyF0nmYWIaxO37Tk6s4U6mPbBhTVu7W0> 9. Benefits of forest kindergartens: improved immunity, self-confidence, improved brain function, etc., see [https://en.wikipedia.org/wiki/Forest\\_kindergarten](https://en.wikipedia.org/wiki/Forest_kindergarten) Emma Marris "we have to let children touch nature, because that which is untouched is unloved" [https://www.ted.com/talks/emma\\_marris\\_nature\\_is\\_everywhere\\_we\\_just\\_need\\_to\\_learn\\_to\\_see\\_it/transcript#t-940244](https://www.ted.com/talks/emma_marris_nature_is_everywhere_we_just_need_to_learn_to_see_it/transcript#t-940244). **Conclusion:** Basing on scientific evidence, the solutions suggested here – such as encouraging regular physical activity outdoors (also for symptomless quarantined people), frequent ventilation with fresh air, and more careful use of antipyretics – can markedly help to reduce the rate of transmission of COVID-19. I hope that this outline will be discussed and refined in the future, to improve public health worldwide. I am very grateful to all the researchers who provided the available scientific evidence as well as my family members and friends who

have discussed it with me. All this has greatly contributed to development of this strategy. As explained in my earlier article (13), close cooperation is urgently needed now, so we must focus on searching for solutions, rather than for people to be blamed. I wish the present terribly difficult situation would lead not only to human suffering but could also urge us to change our priorities and show more respect for other people, our own organisms, the beauty of nature, and our Creator.

**Keywords: the Three Cs Strategy, Physical Activity Outdoors.**

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## “SWEP 2020” CONFERENCE: “Study Design and Editing of Medical Journals” ABSTRACTS

### The Basic Principles of Editing Biomedical Scientific Journals

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#### ABSTRACT

**Background:** There is great need to improve editing of medical journals, both on regional and global level (1-3). **Objective:** The aim of our article was to establish main principles of editing biomedical scientific journals based on evidence found through systematic search of scientific literature (4-9). **Methods:** The evidence for writing this Guideline was systematically searched for during June 2020 in the PUBMED and GOOGLE SCHOLAR databases. The inclusion criteria were: original studies, systematic reviews, invited expert opinions, guidelines and editorials. The exclusion criteria were narrative reviews and un-invited opinion articles. **Results:** In total 11 recommendations were made, based mostly on A and B class of evidence. The editors should educate potential authors and instruct them how to structure their manuscript, how to write every segment of the manuscript, and take care about correct use of statistical tests. Plagiarism detection softwares should be used regularly, and statistical and technical editing should be rigorous and thorough. International standards of reporting specific types of studies should be followed, and principles of ethical and responsible behaviour of editors, reviewers and authors should be published on the journal's web site. **Conclusion:** Evidence-based principles of editing biomedical scientific journals should be followed by chief editors of the journals as a prerequisite of the journals' quality improvement.

**Keywords:** scientific journals, editing, publishing, basic principles.

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## The Importance of Adequate Research Design in Biomedicine

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### ABSTRACT

**Background:** Recent studies have showed that large proportion of published research in biomedical journals suffer from methodological errors that question validity of the results (1-4). **Objective:** The aim of this article was to direct attention of potential researchers to key elements of adequate research design. **Methods:** This Editorial contains description of five most important steps and phases which are obligatory to use in process of making of the appropriate and qualitative research design for providing study investigation in biomedical research (5-7). **Results and Discussion:** Designing, i.e. planning a study in biomedicine has five essential stages that has to be completed if one wants to avoid methodological errors. The first stage is setting research question with three parts: independent variable, dependent variable (outcome) and study population. More detailed determination of the study population with inclusion and exclusion criteria is a second stage. The third stage is calculation of the study sample size and choice of sampling method. Closer description of the study variables with accent on methods of their measurement is the following step, and the final one, fifth stage, is deciding whether the study will be experimental, undertaking control of confounding variables, or observational, with just registering and following the confounders. **Conclusion:** If all five essential steps are completed avoiding introduction of any kind of bias, the study that was designed will be most likely free of critical methodological errors.

**Keywords:** Research design, Biomedicine, Bias, Research methodology.

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## Predatory in Scientific Publication - a Burning Issue in Science

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### ABSTRACT

**Background and Objective:** Predatory publishers and journals, and so-called hijacked or fraudulent journals, are threats to the quality of published articles and waste valuable research and manuscripts when scholars and authors submit and publish their works in these journals. The aim of the study is to identify the features of fraudulent or fake journals, to increase the awareness and warn scholars, especially young researchers, how to recognize and avoid submission of their manuscripts to these journals. **Methods:** Exploring the web blog of Jeffrey Beall and debate about Beall's list of predatory publishers and journals and review of the relevant published literature retrieved from PubMed and trustable Internet sources, as well as personal experience and observations of the author. **Results:** Jeffrey Beall, an American librarian and library scientist from Denver, University of Colorado, has drawn attention to "predatory open access publishing" and created widely known Beall's list, a list of potentially predatory open-access publishers and journals publishing submitted manuscripts promptly without the reviewing process and with a high rate of publication fee. The OMICS International and the "Journal of Forensic Anthropology", renamed in "Journal of Anthropology Reports" are the true examples of predatory publishers and predatory journals. The debate initiated by Jeffrey Beall is continuing in the scientific community with increased number of authors and published articles on this still unresolved issue in the last about 10 years. The features of fraudulent or fake journals, threats and consequences presented by other authors have been discussed as well. **Conclusion:** Unaware of the detrimental effects associated with publishing in disreputable journals, inexperienced researchers can fall victim to those journals. So far the efforts are directed toward increasing awareness in the scientific community how to differentiate between trustworthy and reliable journals and predatory ones, as well as the authors and readers to avoid and completely boycott predatory journals. Continuous education of authors, both the existing and the newly-emerging wave of scholars, must be the

purpose and the imperative of the academic community. In order to protect the peer review process as a heart of the scientific publishing, the academic and scientific community must set the criteria for scientific advancement by not recognizing and valuing the articles published in the predatory journals.

**Keywords: predatory publishers, fraudulent journals, hijacked journals, open access.**

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**"SWEP 2020"**

**TOPICS:**

- Bosnia and Herzegovina experiences related to the COVID-19 pandemic
- Study design and editing of medical journals

**Sarajevo, Nov. 14, 2020.**  
**Hotel Holiday, Sarajevo**

Saturday

# 14 Nov

Hotel Holiday, Una conference hall

<b>09:30-10:00</b>	<b>Asim Kurjak:</b> Has science helped or hindered the battle with the corona pandemic?	<b>15:50-18:00</b>	<b>Short course in research design - five key components / phases:</b>
<b>10:00-10:20</b>	<b>Izet Mašić:</b> COVID-19 pandemic - dilemmas, truths and misconceptions		1. Choice of research topic
<b>10:20-10:40</b>	<b>Osman Sinanović:</b> COVID-19 pandemic: psychiatric and neurological consequences		2. Choice of study type
<b>10:40-11:00</b>	<b>Muharem Zildžić:</b> Nutrition and strengthening of immunity in patients with COVID-19 infection		3. Sample size calculation and sample selection
<b>11:00-11:20</b>	<b>Senaid Trnačević:</b> Organ transplantation in BiH within limiting circumstances caused by COVID-19 pandemic		4. Selection of study variables
<b>11:20-11:40</b>	<b>Emir Mujanović:</b> Organization of the Medical Institute „BAYER“ operation in Tuzla during the COVID-19 pandemic		5. Ethics Committee and regulations
<b>11:40-12:00</b>	<b>Coffee break</b>		<b>Discussion, Conclusions, Recommendations.</b>
<b>12:30-12:50</b>	<b>Sylwia Ufnalska:</b> Strolls and gardening: can they help to fight the pandemic?		<b>Distribution of certificates to course participants.</b>
<b>12:50-13:05</b>	<b>Izet Mašić:</b> How to improve the editing of medical journals?		
<b>13:05-13:20</b>	<b>Slobodan Janković:</b> The importance of adequate study design application in biomedical sciences		
<b>13:20-13:35</b>	<b>Doncho Donev:</b> Predatory in scientific publication - a burning issue in science		
<b>13:35-14:50</b>	<b>Lunch break</b>		



# EASE Guidelines for Authors and Translators of Scientific Articles

SYLWIA UFNALSKA

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Letter to Editor, Received: Nov 05, 2020, Accepted: Nov 25, 2020, doi: 10.5455/ijbh.2020.8.129-130, Int J Biomed Healthc. 2020; 8(2): 129-130

As the editor of EASE Guidelines for Authors and Translators of Scientific Articles (1), first published in 2010 and updated annually till 2018, I did my best to promote more efficient scientific communication worldwide and draw attention to ethical issues related to it. However, there is still a great need to improve the editing of medical journals, as rightly noted by Masic and Jankovic (2). Their effort to provide evidence-based practical guidelines for journal editors is particularly noteworthy. The eleven basic principles of editing biomedical scientific journals formulated by them direct our attention to weaknesses and mistakes of editing and suggest solutions to them. I would like to comment on some of their suggestions here, in relation to the new EASE campaign “Help scientists save time” (3), initiated in October. The campaign is aimed to encourage scholarly journal editors to simplify the technical requirements for initial manuscript submission by means of a revised EASE Quick-Check Table (4, 5), so that scientists could save time for research.

According to the first principle (R1), the abstract and main body of an article should be divided into five sections: “Background, Objective, Methods, Results and Discussion (full text)/Conclusion (abstract), or abbreviated – BOMRAD”. In fact, a similar structure of abstracts has been recommended in EASE Guidelines since 2010. However, in the currently prevalent IMRAD structure of the main part of manuscripts, authors often did not formulate their objectives properly, so the new BOMRAD structure may indeed help to solve this problem. This suggestion deserves to be discussed by the EASE Council before publication of the next editions of both EASE Guidelines and EASE Quick-Check Table.

The second principle (R2) is: “Basic tutorial for writing a scientific paper should be available to potential authors”. This seems to be a very good idea, and some tutorials already available online could be recommended by each journal, to aid authors in proper manuscript preparation. According to the next principle (R3), “Readability of submitted manuscripts should be checked and English language experts should be engaged to edit the manuscripts and increase readability”. The comment about use of validated indices like Gunning’s and Flesch’s, eg with Right Writer software, could truly help to detect less comprehensible manuscripts. However, the indices require

careful judgment, so authors’ opinions and explanations must be taken into account.

I agree also with R4: “Statistical Editor with excellent statistical expertise who will check and edit or request editing statistical aspects of submitted manuscripts should be a member of editorial team” as well as R5: “Technical editing of manuscripts between acceptance and publication should be strict and intensive”. The subsequent recommendations are valid, too: “R6. Editors of medical journals should be trained in editing manuscripts and journals as a whole” as well as “R7. Principles of ethical and responsible behaviour of editors, reviewers and authors should be written in accordance with the Committee on Publication Ethics (COPE) best practices and published on a journal website”.

A comment to the next recommendation (R8), about the requirement to check plagiarism by validated software, is particularly important: „Positive results should be confirmed by manual check”. In fact, some degree of repetition in manuscripts may be necessary for various reasons, so manual check and careful decisions are needed. Considering principle R9, that “Database on which the submitted manuscript is based on should also be submitted to the journal as supplementary file”, it must be remembered that all patient data must be anonymized before submission.

A comment to recommendation R10, about the need to follow international standards of reporting various types of medical studies, emphasizes: “Editors should ensure adherence through double check made by reviewers and the editor themselves”. Last but not least, principle R11 stresses that the Editorial Board of each journal should have balanced proportions of male and female members. This is consistent with the SAGER Guidelines (6).

In my opinion, the eleven principles of editing biomedical scientific journals, beside the ten “Golden rules for scholarly journal editors” published a few years ago (7), provide useful tips and may aid in improving the efficiency and quality of scientific publishing (8).

- **Author’s contribution:** Author S.U. was involved in all steps of preparation this letter to editor including final proofreading.
- **Conflict of interest:** None declared.

- **Financial support and sponsorship:** Nil.

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The screenshot shows the EASE website interface. At the top, there is a navigation menu with items like 'About Us', 'Membership', 'Committees', 'Publications', 'Guidelines & Tools', 'EASE Events', and 'Networking'. Below the menu, the main heading reads 'EASE Guidelines for Authors and Translators of Scientific Articles to be Published in English'. The page content includes a description of the guidelines, a list of languages available (English, Arabic, Bangla, Bosnian, Bulgarian, Chinese, Croatian, Czech, Dutch, Estonian, Finnish, French, German, Greek, Hungarian, Indonesian, Italian, Japanese, Korean, Persian, Polish, Portuguese (Brazilian), Romanian, Russian, Serbian, Slovenian, Spanish, Turkish, and Vietnamese), and a list of three important improvements in the latest edition: an added sentence encouraging ORCID ID registration, an added sentence about formulating the hypothesis in the introduction, and the updated term 'self-plagiarism' replaced by 'content recycling'. There is also a 'Join Now!' button and a section for 'Upcoming Events' listing the 15th EASE Conference, the 36th International Geological Congress, and the International Congress on Peer Review and Scientific Publication.

# Organ Transplantation in Bosnia and Herzegovina Within Limiting Circumstances Caused by COVID-19 Pandemic

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Letter to Editor, Received: Sep 15, 2020, Accepted: Oct 01, 2020, doi: 10.5455/ijbh.2020.8.131-132, Int J Biomed Healthc. 2020; 8(2): 131-132

I failed to present my lecture, probably due to technical reasons, planned for October 14, 2020 at a video conference organized by the Academy of Medical Sciences, which was dedicated to the current events in the pandemic COVID-19 (1). Title of my presentation was: Organ Transplantation in Bosnia and Herzegovina within Limiting Circumstances Caused by COVID-19 Pandemic.

Organ transplantation at the time of the COVID-19 pandemic is very difficult to realize in all aspects of this method of treatment. Difficult communication, limited possibilities of diagnosis and accommodation, treatment and monitoring of patients-special conditions and procedures for testing, processing and treating patients have been created (2-11).

The aim of this Letter to Editor is to describe the current situation about organ transplantation in Bosnia and Herzegovina, regarding limited conditions caused by COVID-19 pandemic and describe the current problems in this field.

A large group of doctors in Bosnia and Herzegovina is trying to maintain an organ transplant program as the most effective and sophisticated form of treatment for terminal liver and kidney damage. The number of patients on dialysis is increasing every year in the world by an average of 7% and in our country that number is maintained at a level between 2600 and 3000. The costs of dialysis are huge, and only for dialysis machines spare parts, these costs amount to about 50 million KM (convertible mark) annually.

The costs of dialysis are on average 4 times higher than the costs of patients with a kidney transplant, and the quality of life is incomparable. University Clinical Center Tuzla is a leader in organ transplantation in Bosnia and Herzegovina for the past 20 years, and only in Tuzla a liver transplant can be performed. The source of organs for transplantation in the world are donors with proven brain death. In our country, the number of such transplants is very small, and the needs of patients are huge. From January to the end of March 2020, only 4 kidney transplants were performed in our country, two from donors with proven brain death, one related and one un-



Figure 1. The kidney transplants performed in Tuzla with a team led by professor Mladen Knotek MD, PhD from Zagreb



Figure 2. A few very complicated kidney transplants were successfully performed on 8 children

related to the patient, one liver and two corneas. After March 2020, and by the end of November 2020, no organ transplants were performed in the conditions of the COVID-19 pandemic.

In other countries, especially in Croatia, about 170-180 different transplantations have been performed. With scarce data both in our country and in the world, high mortality in the conditions of a pandemic of dialyzed and kidney transplant patients stands out. According to the recommendations of the medical profession, transplants should be performed in a pandemic, respecting the protocol that the donor and recipient must be negative for COVID-19 on two separate tests, and that the personnel who will perform the transplant must also be negative. Everything else remained the same in the procedures as before, but with greater caution.

The Renal Registry in Bosnia and Herzegovina partici-



pates with ERA-EDTA in Europe in collecting data on dialysis and transplant patients in the context of the COVID-19 pandemic, and the results are published quarterly. All countries that have a developed transplant program have one umbrella organization that deals with all aspects of organ transplantation. In our country, there is a waiting list only in Federation of Bosnia and Herzegovina, while in the Republic of Srpska and the Brcko District there is no program, so patients do not have any opportunity to receive an organ from a donor with proven brain death.

Even without the COVID-19 pandemic, there were, and still exist, numerous organizational difficulties in this area. We have doctors who can perform most organ transplants, there is space and equipment, as well as appropriate medications and experience, and no transplantations are performed. We point out organizational problems in the conditions of a pandemic, calculating that there will be awareness in state bodies that, finally, organ transplantation will become a priority at the state level. We must all be on the same side for the sake of huge financial savings in health care, for the development of the medical profession, and other supporting disciplines, while the kidney transplant patients return to normal life activities and joys. The kidney transplants performed in Tuzla with a team led by Professor Mladen Knotek MD, PhD from Zagreb (Figure 1), a longtime associate of the University Clinical Center in Tuzla, are very complicated kidney transplants that were successfully performed on 8 children (Figure 2). Unfortunately, compared to the previous period, the number of transplants in Bosnia and Herzegovina is negligible.

- **Author's contribution:** Author S.T. was involved in all steps of preparation this letter to editor including final proofreading.
- **Conflict of interest:** None declared.
- **Financial support and sponsorship:** Nil.

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# COVID-19: a Neurosurgeon's Personal Story of 2020

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On September 9-12, 2019, I traveled to Beijing, China for the World Congress of Neurosurgery. I was eager to attend the biggest event of my profession for two reasons. One was my nomination for second vice-president of the World Federation of Neurosurgical Societies (WFNS). The second reason was to learn about Chinese culture for the first time in my life. I was honored to be elected for an officer position of the WFNS and I tremendously enjoyed the grandiosity of the Great Wall of China (Figure 1), the Forbidden City, and Summer Palace; I also enjoyed trying authentic Chinese food.



**Figure 1.** Visit to the Great Wall of China with My Esteemed Colleagues, Professors Ossama Al-mefty (Harvard University, Boston, MA) and Ugur Ture (Yeditepe University, Ankara, Turkey)

Little did I know that 700 miles away, in the city of

Wuhan, there was trouble brewing. Upon return home, we started hearing news about the COVID-19 virus and its spread across Wuhan, China and subsequent slow infiltration from Asia into Europe and beyond. I was devastated to see pictures, particularly from two countries (Iran and Italy) with overwhelmed hospitals and medical personnel, lack of personal protective equipment and respirators, cases of severe illness, and death in the thousands. The great oceans surrounding the United States initially seemed to be a protective cushion against the spread of the virus to my country. Suddenly, dreaded news from Seattle, WA emerged – the virus had arrived in the U.S. Still, the distance between Seattle, WA and my hometown, Memphis, TN, seemed to be a comfortable barrier.

In February 2020, I was invited give an honorary lecture dedicated to Professor Nurhan Avman in Ankara, Turkey (Figures 2 and 3). My colleagues from Turkey communicated that they are excited for my arrival and reassured me there were zero cases of COVID-19 in Turkey. Again, I visited Turkey, gave the lectures, and was mesmerized by the historical wonder of Cappadocia.

Figure 2.

Figure 3. Back in my home country, the virus spread like wildfire throughout the U.S., shortly arriving to Tennessee just upon my return. The state became overwhelmed and the governor initiated a stay-at-home executive order on April 2<sup>nd</sup>. Our neurosurgical program became limited to only emergency cases (Figure 4), while dozens and dozens of already scheduled elective surgeries had to be indefinitely postponed. My personal research revealed that there is no efficient strategy against the virus except for the following: wear a mask and eye shield/glasses, keep a distance, and frequently wash/disinfect your hands. I decided thereon that I would only wear N95 masks and will not take it off from the moment I leave my house to the moment I come back save for eating lunch in my office alone after thoroughly washing and disinfecting my hands. Surprisingly, in my practice, the number of overall operating cases remained the same as previous years although they were at times emergent cases. Needless to say, neurosurgical disease does not



Prof. Dr. Nurhan Avman

Small text block below the portrait of Prof. Dr. Nurhan Avman, likely containing his biography or a list of achievements.



Prof. Dr. Ali Krişt, M.D.

Small text block below the portrait of Prof. Dr. Ali Krişt, M.D.



Prof. Dr. Kenan Arnautovic

Small text block below the portrait of Prof. Dr. Kenan Arnautovic.



Figures 2 and 3. Visiting Professorship in Ankara, Turkey (Left to Right: Professors Krişt, Caglar, Arnautovic and Dogan)



Figure 4. Operating with My Residents During COVID-19

discriminate against time or place. I continued to work hard despite the pandemic; every day, I psychologically encouraged myself to keep up the pace and remained focused.

Early on, our hospital installed a policy of testing every patient upon arrival to the hospital, especially in potentially operative conditions. Therefore, we were always fairly confident if a patient we were operating on had COVID. However, problems started to arise when people I worked closely with, such as my nurse, medical assistant, and nurse practitioner, who were all people that I had close contact with for a prolonged period of time, tested positive for COVID. Although both parties were protected with PPE in all instances, the risk was real. At first, I was anxious and frankly scared of getting COVID-19 after my exposures, but then, as time passed, it assured me that wearing PPE as religiously as I did and maintaining the aforementioned strategy seems to work. As time passed, I was assured more and more. Needless to say, I was tested a dozen times, every couple of weeks and remained negative so far. We continued to operate, and once restrictions were lifted, we were doing cases almost as pre-pandemic.

Personally, I grieved the loss of many colleagues, co-

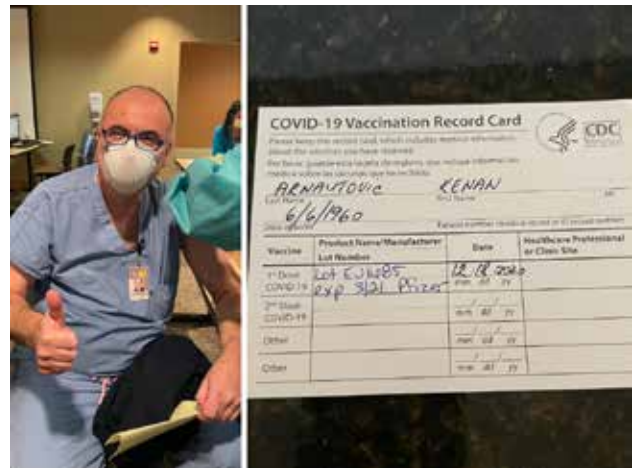


Figure 5. Receiving the first dose of the vaccine on December 18, 2020

workers, friends, and relatives. This extraordinary year has robbed me from the things I love the most – traveling, visiting with friends and family, and my social life. I did maintain some trace of social life by going to restaurants on Fridays and Saturdays with my wife under the appropriate precautions. The other escape to freedom was writing dozens of scientific publications that piled up on my desk for years and were waiting for the appropriate time to be completed. 2020 turned out to be the most productive publishing year of my life.

Furthermore, the medical and neurosurgical community bridged the lack of travel and in-person conferences with online lectures and seminars. I was honored to take part in Days of the Academy of Medical Sciences of Bosnia and Hercegovina in November 2020 under the leadership of Professor Izet Masic. I thoroughly enjoyed the presentations of Professors Kurjak, Masic, Sinanovic, Zildzic, Trnacevic, Mujanovic, Jankovic, and Donev (1-5).

And then, out of nowhere, expected, but surprising, a salvation came to the horizon. A vaccine for COVID-19 was released. It was quickly distributed throughout the U.S. First, Pfizer (New York, NY) on December 11, 2020 and Moderna (Cambridge, MA) on December 18, 2020. I was fortunate to be one of the first recipients of the Pfizer vaccine, receiving my first dose on December 18 (Figure 5). For 2 days, I felt soreness in my arm and feverish, although I did not have a fever. I am scheduled to get the



second dose on January 18 and feel much more confident now.

Taking vengeance against the disease, I decided to take a vacation with my family at Christmastime to Aspen, Colorado, one of my favorite skiing spots in the world. I sincerely hope 2021 will be the year we remember coming out of this nightmare. First, the world must be properly vaccinated to about 70%, providing herd immunity against this horrific virus and then we will see the light at the end of the tunnel.

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# Organization of the Work of the Medical Institute Bayer in Tuzla During the COVID-19 Pandemic

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On the occasion of the 11<sup>th</sup> Days of Academy of Medical Sciences of Bosnia and Herzegovina and 3<sup>rd</sup> Seminar about Writing, Editing and Publishing (SWEP) at Holiday hotel in Sarajevo was organized webinar about COVID-19 Pandemic experiences in Bosnia and Herzegovina. During the webinar members of the Academy from Bosnia and Herzegovina, Croatia, Serbia, North Macedonia, Poland, and USA participated with very interesting presentations (1-5). We also presented lecture about our institution and our professional experiences during pandemic time. Some of important facts which we presented are mentioned in this letter to editor.

Medical Institute Bayer (MIB) is a continuation of the BH Heart Center Tuzla, which was founded in 2008. The goal of establishing the Center was to build a modern, functional hospital that will meet all prescribed norms and standards, and eliminate all limiting factors in the development of cardiac surgery, interventional cardiology and vascular surgery (Figure 1).



Figure 1. Medical Institute Bayer

As part of the development of the Center and the new concept of operation, and in order to cover all new disciplines as well as those that will be developed in the future, in January 2020 the name of the institution was changed to MIB. MIB was named after Dr. Karel Bayer, one of the



Figure 2. Dr. Karel Bayer (1850-1914) (6)



Figure 3. MIB – Reception



Figure 4. MIB–Intensive Care Unit

most important figures in the field of medicine and the first president of the Association of Physicians of Bosnia and Herzegovina (BiH) in 1909 (6) (Figure 2).

The area of the hospital is 11.500 m<sup>2</sup>, with a capacity of 90 hospital beds, intensive care with 12 beds, 4 operating rooms, 3 angio rooms, CT room, 11 clinics and laboratories (Figures 3 and 4).

Within the MIB there is a 4-star hotel, a modern restaurant and a conference hall with a capacity of 120 seats (Figures 5 and 6). MIB has 170 employees: 35 doctors of medicine, 80 nurses and technicians with the remaining technical staff.





Figure 5. MIB- Hotel



Figure 6. MIB. Conference hall



Figure 7. Article from local newspaper

The daily scope of work is 2 cardiac surgery, 1 vascular operation, 8-10 coronary angiography, 3-5 coronary stents, 1-2 electrophysiological interventions. The largest number of patients are from the Federation of BiH, the Brcko District, the Republika Srpska and the region. Since its establishment 12 years ago, MIB is still the Center with the largest number of cardiac interventions and cardiac surgeries in BiH.

Currently, the MIB consists of several Centers: Heart Center; Center for General and Interventional Radiology; Center for Gastroenterology; Center for Urology; Center for General, Abdominal and Pediatric Surgery; Center for Internal diseases.

The first recorded case of COVID infection was reported in one nurse in March 2020, shortly thereafter in 7 other employees after which the MIB was placed in a state of iso-



Figure 8. MIB Reception during the COVID-19 pandemic



Figure 9. Triage point



Figure 10. Clinical pathway for COVID-19 patients

lation with enhanced surveillance. Over the next month, the MIB goes through a very difficult period of complete isolation with a strong sense of stigmatization of some ordinary people, which could be explained in part by ignorance and fear, but unfortunately also by some medical workers who quickly became convinced that a pandemic is not something that “only happens to others “ (Figure 7).

After the MIB was emptied, the rehabilitation of the facility began, which included measures of intensified dis-



infection of the entire institution, all rooms, all vehicles of the center and access roads, after which the MIB was put in a state of so-called “vacation facility”, lasting 15 days. All MIB employees were tested for COVID-19 before re-entering the facility. Employees who entered the MIB after testing, were required to have personal protective equipment (mask, gloves, etc.) and all in accordance with the recommendations (Figure 8).

Upon entering the Institution, they crossed the disinfection barrier and disinfected their hands with a disinfectant placed at the entrance. Patients with symptoms of the underlying disease, before arriving at the MIB with the necessary medical documentation, are required to provide evidence that they have been tested for COVID-19 infection. Prior to patient entry, authorized staff at the triage point perform patient triage measures, complete an epidemiological form for each patient, and measure body temperature (Figure 9). The patient who then enters the MIB is obliged to have personal protective equipment (mask, gloves, socks). COVID-19 positive patients are treated as life-threatening-extremely urgent patients (since there is no possibility of testing).

From entering the Institution to leaving it, it is obligatory to act according to the Protocols for the treatment of COVID-19 positive patients (7-9). If COVID-19 infection is confirmed in these patients, those patients are transferred to the so-called COVID ward, after which preventive intensive disinfection of the rooms in which the patient stayed is performed (Figure 10).

The protection of staff is clearly defined by a special protocol for the admission and treatment of patients during a pandemic, which clearly defines the necessary protective equipment, rules for dressing and undressing, as well as rules for working in special conditions such as operating rooms (10-12).

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# Psychological and Neurological Manifestations Associated with Covid-19

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**Background:** While the COVID-19 pandemic continues to spread globally, more and more evidences are collected about the presence of psychiatric and neurological manifestations and symptoms associated with this disease. **Objective:** The aim of this short communication is to present some of psychological consequences and neurological disorders associated with the SARS-CoV-2 infections. **Methods:** This is cross-sectional study according to psychosocial and neurological manifestations caused by COVID-19 infections published in papers deposited in most influential on-line databases. **Results and Discussion:** The results show presence of central and peripheral nervous system manifestations related to coronavirus. Neurological manifestations, or NeuroCOVID, are part of the COVID-19 clinical picture, but questions remain regarding the frequency and severity of central nervous system symptoms, the mechanism of action underlying neurological symptoms, and the relationship of symptoms with the course and severity of COVID-19. **Conclusion:** The review of the published papers shows that although more and more papers are reporting neurological and psychiatric manifestations associated with COVID-19, many items remain unclear and this uncertainty calls for a global action that requires close co-ordination and open-data sharing between hospitals, academic and public health institutions and the fast establishment of harmonised research priorities to face actual and longterm the NeuroCOVID-19 complications and psychological consequences.

**Keywords:** COVID-19, Neurological disorders, Psychological consequences.

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## 1. BACKGROUND

Infection with the new corona virus (SARS-CoV-2) was first registered in December 2019 in China, and then later spread rapidly to the rest of the world. On December 31, 2019, the World Health Organization (WHO) informed the public for the first time about causes of pneumonnia of unknown origin, in the city of Wuhan (Hubei Province, China), in people who were epidemiologically linked to a seafood and wet animal whole sale local market in Wuhan. Coronavirus disease, called COVID-19 (Corona virus disease 2019), after China quickly spread to most countries in the world, and the WHO on March 11, 2020 declared a pandemic with this virus (1). In Bosnia and Herzegovina, the first infected person was registered on 5.3.2020 in Banja Luka, and in the Federation of Bosnia and Herzegovina on March 9, 2020 in Konjic.

## 2. OBJECTIVE

The aim of this short communication is to present some of psychological consequences and neurological disorders associated with the SARS-CoV-2 infections, and to emphasize the need a global action that requires close co-

ordination and open-data sharing between hospitals, academic and public health institutions and the fast establishment of harmonised research priorities to face actual and longterm the NeuroCOVID-19 complications and psychological consequences.

## 3. METHODS

This is cross-sectional study regarding to psychosocial and neurological manifestations caused by COVID-19 infections based on facts described in published scientific papers searched in most influential on-line databases (PMC, Pubmed, Scopus, etc) in the year 2020.

## 4. RESULTS AND DISCUSSION

### Involvement of the central nervous system

The high pathogenicity of coronavirus (CoV) infection is well known from previous epidemics – Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV-1 and Middle East Respiratory Syndrome (MERS) caused by MERS-CoV. The new coronavirus, SARS-CoV-2, has a high level of sequential similarities to the SARS-CoV-1 and uses the same receptors when it enters the human body

(angiotensin-converting enzyme 2/ACE2)(2-4) The MERS-CoV virus enters via dipeptidyl peptidase 4 (DP4), which is present in the lower respiratory tract, kidneys, small intestine, liver, and immune system cells (5-6). We do not yet know the exact route by which SARS-CoV or MERS-CoV enters the central nervous system (CNS). However, a haematological or lymphatic pathway does not appear to be possible, especially in the early stages of infection, since viral particles are not detected outside nerve cells in infected brain areas (7-9). On the other hand, there is evidence that coronaviruses attack peripheral nerve endings and reach the CNS via nerve synapses (10, 11).

Experiments on mice have demonstrated that SARS-CoV probably enters the brain via the olfactory bulb, and then spreads to other specific parts of the brain such as the thalamus and brainstem through the olfactory nerves. Similar was demonstrated for MERS-CoV. Interestingly, MERS-CoV was infectious in small doses only to the brain but not to the lungs and this brain infection correlated with high mortality in experimental mice. All these studies indicate that the brainstem is one of the highly susceptible areas for infection with SARS-CoV and MERS-CoV viruses. Although this hypothesis requires additional validation for SARS-CoV-2 infection, the fact that almost 50% of COVID-19 patients have neurological problems including epilepsy, ischemic and hemorrhagic stroke, cannot be ignored (12-14). COVID-19 results in neurological damage likely by two mechanisms; hypoxic brain injury and an immune mediated damage to the CNS.

**Neurological disorders**

COVID-19 is primarily a disease of the respiratory system (12). However, SARS-CoV-2, in a number of patients also penetrates the CNS, and apparently could be responsible for fatal outcome in some cases (13, 15, 16).

Site Manifestations	
Central Nervous System	Dizziness
	Headache
	Acute cerebrovascular disease
	Impaired consciousness
	Transverse myelitis
	Impaired consciousness
	Transverse myelitis
	Acute hemorrhagic necrotizing encephalopathy
	Encephalopathy
	Encephalitis
	Epilepsy
Peripheral Nervous System	Ataxia
	Hypogeusia
	Hyposmia,
	Neuralgia
	Guillain Barre syndrome
	Skeletal muscle injury

**Table 1. Neurological complications and manifestations of COVID-19**

The entry of the virus into the brain can lead to neurological (NeuroCOVID-19) and psychiatric manifestations, which are not uncommon, including headache,

anosmia, ageusia, encephalopathy, encephalitis, paresthesia, myalgia, Guillain-Barre syndrome, impaired consciousness, confusion or delirium and cerebrovascular diseases (15, 17, 18). Reported neurological findings can be divided into three categories: central (headache (19, 20), dizziness (19), impaired consciousness, acute cerebrovascular disease, ataxia and seizures), peripheral (hypogeusia, hyposmia) and musculoskeletal (Table 1) (21-23). Moreover, neurological involvement in COVID-19 corresponds to three situations: a) neurological manifestations of viral infection, b) post-infective neurological complications, and c) infection in patients with neurological co-morbidity (24). According to the study of colleagues from China (18), based on the analysis of 214 hospitalized patients in three hospitals in the city Wuhan (with confirmed COVID-19 infection), 6 of 214 patients had either ischemic or hemorrhagic strokes, although it was not reported whether the strokes occurred before or after SARS-CoV-2 infection. The most common CNS symptoms reported were dizziness (36/16.8%) and headache (28/13.1%). Furthermore, a retrospective case series from China found that 22% of people who died from COVID-19 experienced delirium compared with 1% of people who recovered (25).

Multiple cross-sectional studies have demonstrated that the incidence rate of olfactory dysfunction in COVID-19 patients varies from 33.9-68% with female dominance (26). Myalgia and muscle injury were reported in 10.7% of the cases in Wuhan (18) and rhabdomyolysis has been reported in another case from Wuhan (27). Many patients experienced hyposmia or anosmia, dysgeusia, dysarthria and either allodynia or acroparesthesias (21). So far eight cases of COVID-19 associated GBS have been reported from China, Iran and Italy (23, 28).

Given the global dimension of the current pandemic and the high transmissibility of the SARS-CoV-2 virus, the evidence that already exists about the association between this virus and the CNS, raises concerns about the potential long-term effects of COVID-19 on the CNS. The authors propose monitoring of patients who have survived COVID-19, including careful imaging, laboratory, and clinical neurological evaluation, to determine the extent to which the interrelationship between systemic infection and CNS infection leads to CNS damage and neurological disorders. From the current point of view, it seems that in COVID-19 survivors, in the coming years and decades, the inflammatory systemic process and/or the inflammatory process of the brain could trigger long-term mechanisms that generally lead to an increase of neurological and neurodegenerative disorders (16).

**Psychiatric/psychological disorders and consequences**

Due to the fact that information about the diseases caused by SARS-CoV-2 (COVID-19) spread very quickly, becoming pandemic even before the virus pandemic (infodemia), and after the disease spread outside China, confirming the remarks that it is very contagious disease, but also a fatal disease, the general public has become very upset



(29, 30). Apart from respiratory and neurological disorders, it was inevitable to expect that such a large pandemic with numerous uncertainties, drastic changes in everyday life among a significant number of inhabitants of the planet, and even our country would lead to psychological difficulties for a significant number of population, including health workers.

Among the first reports is a study by Xiao et al (31) who analyzed the presence of stress symptoms, anxiety and sleep quality, and the impact of social support on these symptoms, in 170 residents in central China during the COVID-19. They found a high level of stress and anxiety, as well as poor sleep quality in most respondents, and a positive correlation in terms of their lower presence with adequate social support. According to a study by Liu et al. (32) who analyzed 285 respondents over the age of 18 in Wuhan and surrounding cities, where the COVID-19 epidemic started in China, a month after the outbreak, symptoms of post-traumatic stress disorder (PTSD) were present in 7% of subjects. Women had significantly more frequent symptoms of re-experiencing, both repression and arousal, and in the domain of cognition and mood. Subjects who had better sleep quality also had fewer symptoms of PTSD. The authors note that this is the first study on this topic and remind that in earlier study done in Taiwan, after the SARS epidemic, the incidence of depressive symptoms in the sample tested was 3.7% (33).

Previous studies have shown that health professionals developed adverse psychological reactions during infection with the SARS-CoV-1 (34, 35). A Toronto study, analyzing the reactions of hospitalized people to SARS and health workers at a large hospital found, that SARS patients showed fear, loneliness, boredom, and anger, and were concerned about the possible consequences of quarantine and infection on members family and friends. They showed concern about fever and insomnia. Employees, on the other hand, expressed fear of their own infection, infection of family members, friends and colleagues. The care (of health care workers) about health care workers as patients was emotionally difficult for them, and uncertainty and stigmatization were highlighted phenomena and topics of conversation, both among patients and among health care professionals (34).

Maunder (36), studying the psychological consequences of the SARS epidemic in the first half of 2003 in Canada, notes that it was an unpredictable traumatic event for health workers in Toronto. It is estimated that 29-35% of health workers have experienced a high level of distress. The nurses were in the greatest distress, then those who had contact with SARS patients and those who had children. The lessons they have learned are: efforts are needed to mitigate the psychological impact of actions in controlling infection, especially the interpersonal distance that these actions have promoted; effective risk information and education is a priority in the early stages of the epidemic; health professionals can play a role in influencing good media reporting patterns, that can increase or decrease the general morale of the population; health

workers need to have psychological support within the health system as well as clear practical support that facilitates their hard work during an epidemic. High scores on the impact event events in nurses, who had contact with SARS patients, and significant negative impact of social isolation and fear for health, were reported in another study from Toronto (37).

Huang and Zhao (38) recently published the results of study, conducted during the COVID-19 epidemic in China, based on an online cross-sectional survey that included 7,236 volunteers. They determined the overall prevalence of generalized anxiety disorder in 35.1%, depressive symptoms in 20.1%, and sleep quality disorder in 18.2%. Compared to other professionals, health workers were more likely to have poorer sleep quality. Age less than 35 years and focusing on the COVID-19 pandemic (TV, internet cell phone, thinking about infection and consequences) for more than three hours a day was associated with greater anxiety, and in the case of health workers with poorer sleep quality.

In review article, Röhr et al. (39) analyzed 13 studies examining the psychosocial consequences of quarantine measures during the COVID-19 pandemic, noting that these measures were associated with negative psychosocial outcomes, including depressive symptoms, anxiety, anger and stress, PTSD, social isolation, loneliness and stigmatization. Based on the analysis, the authors concluded that quarantine isolation measures during the COVID-19 pandemic have huge negative consequences for mental health; and that preventive interventional measures to reduce psychosocial consequences should be an integral part of the crisis response during pandemic conditions. The second review article, which was based on a review of 28 published papers in journal included in PubMed indexing, and which dealt with the effects of the COVID-19 pandemic on mental health, it was concluded that symptoms of anxiety and depression (16-28%) and stress (8%) are common psychological reactions to the COVID-19 pandemic and are also associated with sleep disorders (40, 41).

## 5. CONCLUSION

The consequences of this pandemic on the overall life of people on the planet are significant and unthinkable. COVID-19 is primarily a disease of the respiratory system, but SARS-CoV-2, the RNA virus that causes the disease, in a number of patients also penetrates the CNS, leading to serious neurological disorders, and apparently it is also responsible for mortality. The entry of the virus into the brain can lead to neurological and psychiatric manifestations, which are not uncommon including headache, anosmia, ageusia, encephalopathy, encephalitis, paresthesia, myalgia, Guillain-Barre syndrome, impaired consciousness, confusion or delirium and cerebrovascular diseases. Psychosocial consequences as well as consequences for mental health are also significant, both for the general population and especially for health workers of all profiles. Many items remain unclear and this

uncertainty calls for a global action that requires close coordination and open-data sharing between hospitals, academic and public health institutions and the fast establishment of harmonised research priorities to face actual and longterm the NeuroCOVID-19 complications and psychological consequences.

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- **Conflict of interest:** *None declared.*
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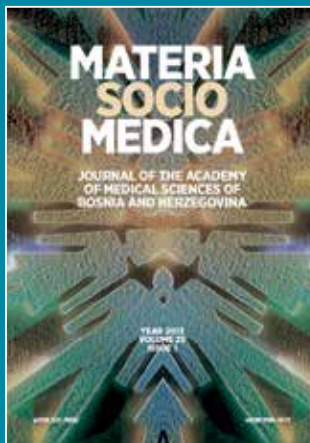
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